THE 1946 YEAR BOOK of GENERAL MEDICINE

AUGUST 1945 — JUNE 1946

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This volume is one of the 13 comprising the Practical Medicine Series of Year Books founded in 1900 by G P Head M D and C J Head and published continuously since then The complete list follows

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DEPARTMENTS *of the* YEAR BOOK *of* GENERAL MEDICINE

Infectious Diseases

GEORGE F DICK, M D

P ofesso of M d ci U v s ty of Ch go Att di g Phy B ll gs Memo l H p tal

Diseases of the Chest

(E cept g the H a t)

J BURNS AMBERSON M D

P of of Med ci College of Phys c d S g ons Col mb U e ty

Diseases of the Blood and Blood Forming Organs Diseases of the Kidney

GEORGE R MINOT M D S D F R C P

(Ed nb rgh and L don)

Profes of Med c e H rd U e sity D ect Tho d ke Memo l l Labo to y V t g Phy n Bo ton C ty Hosp t l

and

WILLIAM B CASTLE M D S M

M D (Ho) Utrech

Pr f ssor of M dic Ha v d Univ ty As oci te Di ctor Th d ke M mo l Labo tory J ior Vis ting Physici n Bo ton C ty Ho p t l

Diseases of the Heart and Blood Vessels

WILLIAM D STROUD M D

P of o of C diol gy G d ate S hool of Medic U s ty of Pen syl ia

Diseases of the Digestive System and of Metabolism

GEORGE B EUSTERMAN M.D

P of o of Med Un ers ty f M sota (Mayo Foundation) S or Co s lt t n Med e May Clin c

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PART II

IMPORTANT ERRATUM NOTICE

On page 500 of the 1946 YEAR BOOK OF GENERAL MEDICINE in the fourth textual line from the bottom of the page the last word should be milligrams instead of Gm

INFECTIOUS DISEASES



GEORGE F DICK M D

PART I

INFECTIOUS DISEASES

GENERAL CONSIDERATIONS

Effect of Emetine in Bacterial Infections In previous experiments Peter Bernoulli[1] (Univ of Basle) found *emetine in vitro* to have only a very mild disinfecting action a curious phenomenon when considered in the light of its powerful effect in vivo he therefore conducted a number of experiments on animals to determine the cause of this discrepancy The results confirmed the salutary effect of emetine on septic infections and showed that it accelerates formation of agglutinins and spontaneous phagocytosis of leukocytes of the blood Thus the primary effect of emetine in vivo appears to be a general acceleration and positive catalysis of the defense mechanisms of the entire organism

Use of Micro organisms for Therapeutic Purposes Howard W Florey (Univ of Oxford) reviews the many observations made on antibiosis since 1887 especially the voluminous research reported since penicillin became available as a powerful antiseptic that can be introduced into the blood stream The early experimental work done at the University of Oxford showed that penicillin is unique in that it does not harm delicate body tissue even when used in quantities far exceeding the amount therapeutically necessary Furthermore penicillin unlike the sulfonamides is not influenced by the inhibitory factors present in pus and other breakdown products of tissues Hence it has a far wider application than was first supposed Penicillin proved especially valuable in war surgery particularly when it was discovered

(1) S hw Zt h f P th B kt 7 9(105 1944
( ) B t M J 2 635 64 N 10 1945

that it was most effective when given immediately in forward hospitals together with appropriate surgical treatment

Nitrogen Metabolism in Acute Infections Charles M Grossman Thomas S Sappington Belton A Burrows Paul H Lavietes and John P Peters[3] (Yale Univ) studied the effects of diets high in protein and diets supplemented by protein on the wastage of nitrogen which occurs in severe infectious diseases and in surgical conditions The supplementary protein consisted of amigen a hydrolyzate of casein and pork pancreas which was given intravenously to certain patients in a 5 per cent solution with 5 per cent dextrose Balance studies made on 45 patients with conditions ranging from meningococcic meningitis to skin infections and traumatic ruptures of muscle showed no effect from the high protein diets or the supplementary protein The negative nitrogen balances remained until there was a natural reversal Generally after ordinary operations negative nitrogen balances were short lived but their occurrence and duration in acute infections were found to be unpredictable Loss of nitrogen in meningitis was surprisingly large whereas the nitrogen metabolism was not disturbed appreciably in minor respiratory infections

Abundant and adequate diets should be continued in treatment of patients unless it can be shown that a rich diet is harmful to the nitrogen balance

Concerted Antibiotic Effect of Penicillin, Methionine, Threonine and Methionine Sulfoxide on Brucella, Eberthella, Salmonella and Shigella Gregory Shwartzman[4] (Mount Sinai Hosp New York City) reports experiments that show a great enhancement of penicillin susceptibility of highly refractory gram negative organisms when methionine threonine and methionine sulfoxide are added The action of amino acids appears to be synergistic rather than additive Methionine is essential for the enhancement Threonine and methionine sulfoxide

(3) J Cl n I vest g tion 24 523 531 J ly 1945
(4) Scienc 102 148 150 Aug 10 1945

facilitate the effect of methionine after a reciprocal quantitative relationship

Factors Determining Dosage of Penicillin in Treatment of Infections Charles H Rammelkamp and William M M Kirby[5] (Fort Bragg N C) point out that optimal concentrations of penicillin are all that is necessary since larger doses will not raise the drug s anti

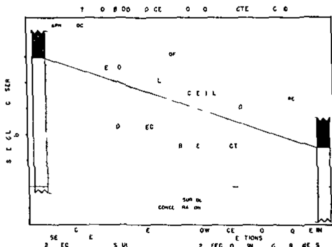


Fig 1 (C u t y f R mm lk mp Ch l H d K b W ll m M M B ll N w Y k Acad M d, 1 656 672 D embe 1945)

bacterial activity A study of the absorption and excretion of penicillin and its diffusion into various body fluids indicates that for adequate and conservative therapy of staphylococcic streptococcic and pneumococcic meningitis both parenteral and intrathecal routes should be used since penicillin apparently reaches the spinal fluid only in small quantities if at all In general diffusion of penicillin into various body fluids and cavities occurs irregularly and is slight Therefore

(5) B ll N w Y k Acad. M d 21 656 6 D mb 1945

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(3) J Clin I nvestigation 4 523 531 July 1945
(4) Science 102 148-150 Aug 10 1945

effects of certain amino acids on the susceptibility of various groups of gram negative aerobic bacilli to penicillin Strains of Escherichia coli and salmonella were used

The susceptibility of both organisms to penicillin was highest in a basal medium devoid of amino acids Blood serum in various concentrations meat infusion broth yeast extract and casein hydrolyzate interfered with penicillin activity apparently because of an antagonism of certain amino acids in these materials Dicarboxyl monoamino acids cystine arginine histidine and hydroxyproline were all capable of suppressing the effect of penicillin on the organisms This antagonism of amino acids is not primarily related to their effect on the rate of bacterial growth it is apparently due to the effect of the acids on bacterial metabolism This conclusion was supported by the significant changes observed in the penicillin susceptibility when Escherichia coli was maintained serially in mediums of varying composition for a number of generations prior to testing namely in basal Gladstone medium alone Gladstone medium containing casein hydrolyzate and meat infusion agar The casein Gladstone substrain possessed the highest susceptibility The meat infusion agar and Gladstone substrains were 1 66 and 3 times more resistant to penicillin respectively than the first substrain Casein hydrolyzate had a higher concentration of antagonistic amino acids than meat infusion broth and the Gladstone medium contained no amino acids Thus the acquired penicillin resistance bore an inverse relation to the concentration of antagonistic amino acids

The antipenicillin activity of amino acids may be reversed significantly by dl methionine However this substance reverses only incompletely the antagonism of materials of mixed composition e g casein hydrolyzate meat infusion broth and serum After addition of methionine methionine sulfoxide and threonine a marked enhancement of penicillin susceptibility of broth

local therapy as well as parenteral injections can be used in infections of pleural pericardial and joint cavities

The relation of concentration of penicillin in the blood stream to the sensitivity of various susceptible organisms as well as to other factors is summarized diagrammatically in Figure 1 The extremes of variation in susceptibility are represented by the staphylococcus and the hemolytic streptococcus Because of the serious nature of infections such as syphilis diphtheria and gas gangrene the organisms causing these diseases should also be regarded as highly resistant therapeutically until more information has been gathered Highly sensitive organisms are the gonococcus and pneumococcus Strains of intermediate sensitivity are represented by the meningococcus Other factors determine the size of dosage namely severity of infection vascularity of area involved and the barriers which must be penetrated by penicillin to come in contact with the infecting organism

Consideration of all these factors should make it possible to plan a rational therapeutic regimen Thus for staphylococcic infections for example injections of 25 000 units every two hours will produce optimal continuous levels in the blood stream whereas for streptococcic infections 15 000 units every three hours is adequate Blood levels which can be more or less constantly maintained with a continuous intravenous infusion for 24 hours used in seriously ill patients are as follows with 100 000 units 0 1 unit per cc with 200 000 units 0 2 unit per cc and with 400 000 units 0 4 unit per cc With a continuous intramuscular infusion the levels are almost identical with those obtained by the intravenous route Subcutaneous administration however produces concentrations only about one half as great as those with the other two methods

Nature of Resistance of Gram Negative Bacilli to Penicillin Gregory Shwartzman[6] (Mount Sinai Hosp New York City) studied the antagonistic and enhancing

(6) J F per Med 83 65 89 J an 7 1946

aside from an occasional slight burning sensation immediately after application Some of the results were excellent Use of the ointment eliminated Proteus vulgaris from an osteomyelitis wound when that organism was rapidly destroying recent skin grafts It did this promptly after its application although previous treatment with streptomycin had failed A gram negative micrococcus was eliminated from another compound fracture wound when granulations did not develop properly After its application granulations grew and permitted skin grafting within a few days Its application further eliminated a typhoid bacillus Pseudomonas aeruginosa and Escherichia coli in other cases

Penicillin Treatment of Serous Cavity Infections I W J McAdam J P Duguid S W Challinor and A McCall[5] (Univ of Edinburgh) used the biologic method for estimating penicillin concentration in this method the limiting dilution of the fluid which completely inhibits the growth of the standard strain of Staphylococcus aureus (Oxford H strain) is determined Fluids examined were serum pleural pericardial peritoneal synovial and cerebrospinal fluids and pus from abscess cavities Complete bacteriostasis to the standard Staphylococcus aureus in undiluted fluid is considered the minimal therapeutic level based on clinical experience in 40 cases of acute hematogenous osteomyelitis and in infections with penicillin sensitive Staphylococcus aureus

The passage of penicillin from blood to peritoneal fluid and from peritoneal fluid to blood was investigated to determine the most effective route of administration for peritoneal cavity infections Effective treatment can be given with two or three intramuscular injections of 100 000 units daily or by a continuous intramuscular infusion of 100 000 units a day

Because it was believed that penicillin given systemically could not pass the pleural barrier pleural cavity infections were formerly treated by local injection of

(8) La c t 2 843 848 D 29 1945

cultures of brucella eberthella salmonella and shigella occurred apparently due to the ability of this amino acid mixture to reverse effectively the action of the antagonists present in the cultures Methionine was essential for this enhancement and threonine and methionine sulfoxide facilitated the effect of methionine following a reciprocal quantitative relation

Treatment of Mixed Infections with Penicillin Frank L Meleney Balbina A Johnson Edwin J Pulaski and Frances Colonna[7] (Columbia Univ) point out that certain mixed infections do not respond satisfactorily to penicillin therapy primarily because of the presence of penicillinase an agent of enzymatic nature which is produced by the large group of aerobic non-spore forming gram negative rods such as the coliform, the *proteus and the Pseudomonas bacilli and which inhibits* or slows down the drug s bacteriostatic action The authors therefore studied many chemical compounds to discover an antibacterial agent effective against the gram negative organism and yet compatible with penicillin The substance which seemed most nearly to fill all requirements is parachlorophenol Other substances tested were 9 aminoacridine hydrochloride and 5 nitro 2 furaldehyde semicarbazone these were not effective against Pseudomonas aeruginosa

An ointment was made from parachlorophenol by melting together 45 parts of carbowax 4 000 with 55 parts of propylene glycol either over a free flame or in a hot water bath When thoroughly mixed they were sterilized in a dry oven at 140 C for four hours and then cooled At the beginning of solidification at 40 C 1 000 units per Gm penicillin and 0 25 per cent of parachlorophenol were added The ointment was then incorporated sterilely into fine meshed gauze and placed in a pile of 50 or more in a container and kept in the refrigerator The ointment was then used in surgical infections There was no local or general toxic reaction

(7) J A M A 130 121 124 Jan 19 1946

aside from an occasional slight burning sensation immediately after application Some of the results were excellent Use of the ointment eliminated Proteus vulgaris from an osteomyelitis wound when that organism was rapidly destroying recent skin grafts It did this promptly after its application although previous treatment with streptomycin had failed A gram negative micrococcus was eliminated from another compound fracture wound when granulations did not develop properly After its application granulations grew and permitted skin grafting within a few days Its application further eliminated a typhoid bacillus Pseudomonas aeruginosa and Escherichia coli in other cases

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penicillin with unsatisfactory results The authors therefore investigated whether adequate penicillin concentration in empyema could be achieved by systemic administration and found that bacteriostasis could be maintained Hence they suggest that for cases of localized intrapleural infections penicillin be given either by continuous intramuscular infusion of 100 000–200 000 units daily or by two or three intramuscular injections of 100 000 units daily together with establishment of adequate drainage by rib resection

Examination of the passage of penicillin from the subarachnoid space into the spinal fluid showed that in cases of meningitis or postmeningitic encephalitis systemic administration of penicillin resulted in an adequate concentration this was *not true for normal subjects* In one early case of meningitis moreover intramuscular injection did not produce sufficient concentration of penicillin in the cerebrospinal fluid The authors therefore conclude that systemic administration of penicillin alone is not sufficient but should be combined with intrathecal administration

Investigations showed that for synovial cavity *inflammations* penicillin is most beneficial when given systemically so that it reaches all parts of the joint cavity making frequent aspiration unnecessary For septic arthritis a dose of 100 000 units a day by continuous intramuscular infusion or single intramuscular injection of 100 000 units two or three times a day is probably adequate When a joint is accessible and aspiration is done for relief of tension local administration in addition to the systemic is probably best

The penetrability of the pericardial cavity by penicillin was tested in only one case of suppurative pericarditis with staphylococcic septicemia The patient was given 180 000 units of penicillin daily by continuous intramuscular drip only a small amount of penicillin passed into the pericardial fluid which was completely bacteriostatic only when undiluted After local administration of

30 000 units the fluid was bacteriostatic in a dilution of 1 16 000 this level was maintained for six hours In 24 hours penicillin was not detectable

Pus must be evacuated from abscess cavities if it is under high tension otherwise penicillin will not enter

Effect of Sulfonamides on Action of Penicillin Gladys L Hobby and Martin H Dawson[9] (Columbia Univ) report experiments on the in vitro effect of combined penicillin and sulfadiazine The results obtained depend on (1) concentration of each bacteriostatic agent (2) number of organisms present (3) environmental conditions allowing growth of organism (4) degree of susceptibility of organism to penicillin and to sulfadiazine and (5) the species of organism

When the amount of penicillin is so small that little or no bacteriostatic action is produced sulfadiazine increases bacteriostasis if the organism is sulfadiazine sensitive and is present in small numbers only In this instance the bacteriostatic effect is predominantly due to sulfadiazine When there is enough penicillin to produce definite bacteriostatic or bactericidal effect during the first few hours of incubation but not enough to yield complete sterilization sulfadiazine increases bacteriostasis if the number of organisms present at the end of the sulfadiazine lag period is low Sensitivity of the organism to sulfadiazine enhances this effect When large amounts of penicillin are present the bactericidal action is rapid during the first few hours of incubation Complete sterilization may result before five to seven hour If sterilization is not complete at the end of this time sulfadiazine may prolong the lag period or even slightly decrease the bactericidal rate provided the organism is sensitive to sulfadiazine and is present in small numbers The action of penicillin occurs predominantly at the time of cell division A decrease in the rate of multiplication due to sulfadiazine may therefore decrease the rate at which penicillin acts

(9) J B t 51 44 45 Ap 1 1946

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determining whether a particular body fluid is rendered bacteria free when the patient is under penicillin treatment penicillinase should be used routinely when making such cultures

Criteria of Pathogenicity in Staphylococci On the basis of the coagulase test and hemolysis on sheep blood agar R Christie E A North and Barbara J Parkin found that staphylococci may be divided into three broad groups coagulase positive strains of definite pathogenicity coagulase positive strains of doubtful pathogenicity and nonpathogenic strains The tendency of many strains to throw variants with fewer of the properties characteristic of pathogens than those possessed by the parent strains suggests that the fully pathogenic staphylococcus showing all these properties is the original organism and that as one property after another is lost the organism degenerates to the typical nonpathogen with none of the properties possessed by the typical pathogen The commonest form of degeneration was found to be loss of hemolytic power

In the present study 1 027 strains of staphylococci were tested for ability to produce coagulase hemolysin fibrinolysin and pigment and to ferment mannitol 312 of these strains were tested for pathogenicity to mice It was found that production of alpha toxin is necessary for full pathogenicity A strain may produce coagulase and still be nonpathogenic It may fail to produce beta toxin fibrinolysin or pigment or to ferment mannitol and still be pathogenic If sheep blood agar is used in primary isolation of staphylococci from human beings presence or absence of definite hemolysis will decide pathogenicity Further tests are necessary only when degree of hemolysis is less than that given by the usual pathogenic strains

Studies on the Streptococci ('Enterococci') of Lancefield Group D Serologic and Biochemical Characteristics are reported by G E Foley and S M

( ) A t l J E per B l & M S 24 73 8 Ma h 1946

The data obtained suggest that the combined use of sulfadiazine and penicillin may produce greater bacteriostasis than either alone It has not been proved that the two agents act independently of each other or that one increases the activity of the other That sulfadiazine appears to increase the activity of penicillin against one strain resistant to penicillin alone suggests that penicillin may increase the sensitivity of the bacterial cell to sulfadiazine *Since special experimental conditions have* been necessary to produce the effects described here it is impossible to determine in advance whether or not sulfadiazine will enhance bacteriostatic action of penicillin in human infection

Use of Penicillinase in Cultures of Body Fluids from Patients under Treatment with Penicillin Harry F Dowling and Harold L Hirsh[1] (George Washington Univ) report their experiments with penicillinase *Penicillin in culture medium without penicillinase remained* active for 24 hours or longer and inhibited the growth of sensitive bacteria during this time when sufficient penicillinase was added a therapeutic concentration of penicillin was inactivated within 15 minutes or less permitting the growth of bacteria

These findings are of considerable importance for determining the disappearance and rate of disappearance of bacteria from the blood stream and other body fluids of patients receiving penicillin without use of penicillinase the cultures from the various body fluids were either negative or gave delayed or inhibited reactions In some cultures the organisms did not grow regardless of the presence of penicillinase This was undoubtedly due to the rapidity with which therapeutic doses of penicillin cleared the blood stream and body fluids of susceptible bacteria In three cases of Streptococcus viridans endocarditis the blood was apparently free from organisms in 5–54 hours after the beginning of penicillin treatment *Since there is no other way of*

(1) Am J M Sc 210 756 76 D mb 1945

turnover of personnel who came in part from recruiting centers with high incidence of infections and unfavorable winter climate Sulfadiazine was given prophylactically to one half only of the students in daily doses of 1 Gm throughout the training period of 3½ weeks

The first period of chemoprophylaxis with sulfadiazine was quite successful significantly few streptococcic infections occurred in the treated group During a second period in which this type of prophylaxis was not so successful as expected it was found that there was increasing prevalence of strains of group A hemolytic streptococci resistant to sulfadiazine

[In view of the serious lesions described by Lich and others as due to allergic reaction to sulfonamides it seems questionable whether prophylactic use of sulfonamides is justified —Ed]

Studies on Streptomycin in Man Absorption Distribution, Excretion and Toxicity Harold A Zintel Harrison F Flippin Anna C Nichols Marjorie M Wiley and J E Rhoads (Univ of Pennsylvania) studied the behavior of a single dose of streptomycin and of continuous administration Twenty patients ranging from perfectly healthy to severely ill were given single doses and 18 patients with typhoid fever Rocky Mountain spotted fever brucellosis ulcerative colitis urinary tract infection and Salmonella Oranienburg infection were treated by continuous administration The drug was given in various ways to both groups When taken orally it was dissolved in sterile water and mixed with milk For continuous intravenous administration it was given in a continuous drip of 5 per cent glucose solution When large amounts of streptomycin such as 600 000 units were given intravenously in a single dose the drug was dissolved in 200 cc physiologic saline solution and given over 15–20 minutes For intramuscular injection the drug was dissolved in 1 per cent procaine solution for a concentration of 40 000 or 100 000 units per cc solution

(5) Am J M S 210 4 1 430 Oct 1945

Wheeler[3] (Harvard Univ) The streptococci of this group D have been differentiated into four serologic types by precipitation and slide agglutination tests with type specific antiserums produced in rabbits The group specific substances of types 1 3 and 4 are probably protein while type specificity is determined by the carbo hydrate substances in type 2 the type substance ap parently is a protein Heat resistance supposedly a characteristic of enterococci is not reliable as a criterion for their recognition since only 10 per cent of the strains studied survived exposure to 62 5 C for 30 minutes There was no correlation between heat resistance and serologic type or the inability to ferment mannitol Neither could serologic type be correlated by biochemi cal activity All strains reduced methylene blue by which property they may be distinguished to some extent from streptococci not belonging to the group D organisms

Blood agar was also of limited value in the recognition of group D strains since alpha beta and gamma organ isms were observed within the group No strains pro duced soluble hemolysin The authors suggest that the term beta be applied to those strains which produce soluble hemolysin and the term pseudobeta to those giving only beta reactions on blood agar Such nomen clature would necessitate use of the tube hemolysis test in addition to the standard blood agar test and in ab sence of serologic methods would be valuable in the routine procedures used to identify streptococci How ever serologic classification is still the most reliable method of identification of the various strains

Chemoprophylaxis and Sulfonamide Resistant Strep tococci Douglas S Damrosch[4] reports the results of a controlled program of chemoprophylaxis against hemo lytic streptococcus infections in three small naval train ing schools These infections had previously reached epidemic proportions because of overcrowding rapid

(3) Am J D Child 70 93 99 A g t 1945
(4) J A M A 130 1 4 1 8 J 19 1946

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(5) Am J M S 210 4 1 430 Oct b 1945

The blood level of streptomycin after single intravenous injections is better maintained than is the case with penicillin Detectable amounts were usually present for 6 hours as compared with 2½–3 hours with penicillin even when the intramuscular route was used for the latter drug Excretion of the drug is primarily by the urinary tract when given intravenously subcutaneously or intramuscularly Only 2 per cent of the drug was found in the feces The approximate amount appearing in the urine was 66 per cent this indicates that some of the streptomycin is retained or destroyed in the body When the drug was given orally it was chiefly excreted in the feces since streptomycin passes through the gastrointestinal wall only in very small amounts It appears appropriate therefore to treat those infections in which the pathogenic organisms are found in the gastrointestinal tract as well as in the blood stream by the oral and parenteral routes

After parenteral injection the drug is found distributed in most body fluids blood urine ascitic fluid pleural fluid aqueous humor vitreous humor amniotic fluid and bile Small amounts appeared in the spinal fluid in healthy persons but the spinal fluid of a patient with *Haemophilus influenzae* meningitis contained 25 units per cc

Immediate toxic effects consisted of headache flushes transient urticaria and fever Their severity can be decreased by decreasing the rate of administration Local thrombophlebitis may occur after continuous intravenous administration Liver function tests were made on six patients to determine the effect of a single massive dose of streptomycin No damage to the liver and its function was discovered in fact two patients with liver damage before administration of the drug showed slight improvement in hepatic function Tests of renal function likewise demonstrated no damage to the kidneys The blood picture appeared unharmed and unchanged after administration of streptomycin

SENSITIVITY OF INTESTINAL FLORA TO STREPTOTHRICIN AND STREPTOMYCIN

O SMS S S OF NO M L MI	U M † O I I	O SMS IN S M S OTH I TH (13 DA)	U TS S H C N M FO IN	O C N SMS I S LS M C PTE ST EPTOM C THERAP (10 D)	U I STREPTO M N PE M R I H T O
E ch coli (communior)	10 0	B mesentericus	5	B closteroides	>320
Esch coli (communior)	?0 0	B subtilis	20	B megatherium	>3?0
Salmonella	10 0	B ubtilis	>320	B mesentericus	>3?0
Esch coli (acidi lactici)	? 5	E ch coli (neopolitans)	160	B subtilis	>320
Esch coli (acidi lactici)	10 0	P aeruginosa	80	Staph aureus	>3?0
S lutea	10 0	P aeruginosa	3?0	Gram negative rod (Non lactose fermenter)	>3 0
S dysenteriae	2 5	S marcescens	5		
		S marcescens	80		
		Staph albus	3?0		
		Staph aureus	40		
		Staph aureus	160		

F m l f t l food t (Gm pe 100 Gm) y ll w m l 31 wh l wh t (g d) 30 (t ch l) 10 yb m l 10 l d l m l 7 b s y t 5 H lf m l 2 N Cl 0 5 C CO 0 5 c l 3 c d l 1 1

† U t of t ptoth o t pt my

The blood level of streptomycin after single intravenous injections is better maintained than is the case with penicillin Detectable amounts were usually present for 6 hours as compared with 2½–3 hours with penicillin even when the intramuscular route was used for the latter drug Excretion of the drug is primarily by the urinary tract when given intravenously subcutaneously or intramuscularly Only 2 per cent of the drug was found in the feces The approximate amount appearing in the urine was 66 per cent this indicates that some of the streptomycin is retained or destroyed in the body When the drug was given orally it was chiefly excreted in the feces since streptomycin passes through the gastrointestinal wall only in very small amounts It appears appropriate therefore to treat those infections in which the pathogenic organisms are found in the gastrointestinal tract as well as in the blood stream by the oral and parenteral routes

After parenteral injection the drug is found distributed in most body fluids blood urine ascitic fluid pleural fluid aqueous humor vitreous humor amniotic fluid and bile Small amounts appeared in the spinal fluid in healthy persons but the spinal fluid of a patient with Haemophilus influenzae meningitis contained 25 units per cc

Immediate toxic effects consisted of headache flushes transient urticaria and fever Their severity can be decreased by decreasing the rate of administration Local thrombophlebitis may occur after continuous intravenous administration Liver function tests were made on six patients to determine the effect of a single massive dose of streptomycin No damage to the liver and its function was discovered in fact two patients with liver damage before administration of the drug showed slight improvement in hepatic function Tests of renal function likewise demonstrated no damage to the kidneys The blood picture appeared unharmed and unchanged after administration of streptomycin

pyrazine but not with sulfadiazine These recurrences may possibly be prevented by adoption of different methods of administration or of different amounts of drug and timing of administration because apparently the drug remains in the blood stream only for a very short time

Study to Determine Antibacterial Efficiency of Combined Tyrothricin and Sulfadiazine Richard Kelso and Basil Thompson[8] (Arlington Va) used a mixture of

EXPERIMENTAL DATA ON ANTIBACTERIAL EFFICACY OF TYROTHRICIN AND SULFADIAZINE

O M	C	S UM S		T N		C M N N	
	C l m t P d g	C l m t P d	I h b t y Eff t	C l t R l ng	I h b t y Eff t	C l m t I ad g	I h b t y Effe t
Staph aureus	56	43	+	41	+	35	++
Staph albus	6_	40	+	38	+	36	++
Stre haemolyticus	44	29	++	_7	++	26	+++
Stre faecalis	30	30	0	21	++	21	++
Friedlander s A	48	3?	+	45	0	3o	+
Friedlander s B	87	55	+	88	0	61	+
N intracellularis	29	_4	+	27	0	25	+
N catarrhalis	42	29	+	24	++	30	+
C diphtheriae	28	27	0	19	+	[illegible]	+
C pneumoniae	37	30	+	2	++	24	+
S paratyphi	66	63	0	64	0	63	0
S enterit dis	86	80	0	75	+	84	+
Esch coli	69	64	0	73	0	66	0

these two drugs as a bactericidal agent against the organisms commonly found in the upper respiratory tract ear and infected sinuses The mixture consisted of tyrothricin in a 1 2000 dilution and sodium sulfadiazine in a 2 per cent concentration The organisms were isolated in pure culture and grown and then subjected to tyrothricin-sodium sulfadiazine suspension sulfadiazine alone and tyrothricin alone As shown in the table the combination of the two drugs was more efficacious as an antibacterial

(8) V g M M thly 73 4 5 M y 1946

Influence of Streptomycin and Streptothricin on Intestinal Flora of Mice Dorothy G Smith and Harry J Robinson[6] (Rahway N J) investigated the effect of streptomycin and streptothricin on enteric infections in mice Sulfasuxidine and sulfaguanidine were also used Of the four drugs streptomycin was most effective in both rate and extent of reduction of the numbers of intestinal organisms in mice whereas sulfaguanidine was the more effective of the two sulfonamides

Not only were the numbers of the coliform organisms rapidly and effectively reduced if not eliminated by each of the two antibiotics but also in the case of streptomycin the total flora was strikingly decreased and this reduction was not merely temporary but remained during the treatment period (see Table page 23)

The dose of streptothricin required for effective reduction was one half the toxic dose Its use therefore in human diseases is probably limited but it might be valuable in treatment of enteric diseases in cattle and other animals The dose of streptomycin necessary was much below the toxic dose and this drug may therefore be effective in both man and animals not only therapeutically for enteric diseases but also prophylactically in pre and postoperative treatment of surgical infections

Plague Treatment of Experimental Animals with Streptomycin, Sulfadiazine and Sulfapyrazine N E Wayson and Margaret C McMahon[7] (San Francisco) report on experiments designed to evaluate streptomycin in the therapy of plague induced in mice and guinea pigs by inoculation and in guinea pigs infected by the bites of infectious fleas Results showed that streptomycin has definite value in treatment of white mice and guinea pigs but has less value in treatment of mice after development of bacteremia than in guinea pigs Clinical recurrences were frequent with streptomycin and sulfa

(6) J B t 50 613 6 1 D 1 1945
(7) J Lab & Cl M d 31 3 3 33 M h 1946

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O ism	C N	S um Su		T o- N		C M N	
	Col m t Pe d g	C l m t I d g	I h b t y Eff t	C l t R d g	I h b t y Eff t	C l m t R l g	I h b t y Eff t
Staph. aureus	56	43	+	41	+	35	++
Staph albus	62	40	+	38	+	36	++
Stre haemolyticus	44	29	++	27	++	26	+++
Stre faecalis	30	30	0	21	++	21	++
Friedlander s A	48	32	+	45	0	36	+
Friedlander s B	87	55	+	88	0	61	+
N intracelluları	29	24	+	27	0	3	+
N catarrhalis	4	2	+	24	++	30	+
C diphtheriae	28	27	0	19	+	22	+
C pneumoniae	37	30	+	2	++	24	+
S paratyphi	66	63	0	64	0	63	0
S enteritidis	86	80	0	5	+	84	+
Esch coli	6	64	0	73	0	66	0

these two drugs as a bactericidal agent against the organisms commonly found in the upper respiratory tract ear and infected sinuses The mixture consisted of tyrothricin in a 1 2000 dilution and sodium sulfadiazine in a 2 per cent concentration The organisms were isolated in pure culture and grown and then subjected to tyrothricin–sodium sulfadiazine suspension sulfadiazine alone and tyrothricin alone As shown in the table the combination of the two drugs was more efficacious as an antibacterial

(8) V g M M thly 73 4 25 M y 1946

agent than either of them alone The solution suspension mixture was also relatively stable

Inactivation of Viruses by Radiations D E Lea[9] (Cambridge) reviews recent experiments on inactivation of plant animal and bacterial viruses by gamma rays x rays and alpha rays In sufficiently dilute aqueous solutions the inactivation is mainly indirect i e it is caused by production of ionization in the water rather than in the virus itself If the virus is irradiated dry however or in an aqueous solution of sufficiently high solid content larger doses are required and the inactivation is mainly direct i e the inactivation of a virus particle is due to production of ionization in the particle itself The effect of a given dose increment is independent of previous irradiation of the virus preparation Inactivation of a virus particle is not the cumulative effect of all radiations administered but is due to a single unit action For a given virus the inactivation dose is greater for alpha rays than for x rays and greater for x rays than for gamma rays According to Bonet Maury the vaccinia virus is more sensitive to alpha rays than to x rays Lea and Salaman however find the contrary to be true

A correlation exists between virus size and inactivation dose in the sense of the larger viruses being more sensitive than the smaller viruses The experimental relation between inactivation dose and virus size is compared with the relation calculated on the hypothesis that a single ionization anywhere in the virus particle leads to inactivation Probably not every ionization is certain to lead to inactivation but if attention is confined to viruses of diameter smaller than 100 mμ the diameter calculated on assumption that every ionization in the virus is effective will not be in error by a factor exceeding two

Interference between Viruses in Tissue Culture Edwin H Lennette and Hilary Koprowski[1] (Rio de Janeiro)

(9) B t J R d 1 19 205 212 M y 1946
(1) J E pe M d. 83 195 19 M ch 1946

investigated the influence of one virus on the growth of another in tissue culture using the viruses of yellow fever West Nile disease Venezuelan equine encephalomyelitis and influenza A They found that the 17DD High strain of yellow fever was capable of completely suppressing the growth of both the Asibi strain of the same virus and of the heterologous West Nile virus even when these were added to the cultures in large amounts The 17DD High strain of yellow fever virus and the West Nile virus produced either partial or complete suppression of growth of the Venezuelan equine encephalomyelitis virus depending on the quantity of the latter inoculated into the cultures Both viruses were also able to suppress completely or almost completely the growth of influenza A virus added to the infected cultures in maximal amounts Interference in the reverse direction even with use of small amounts of the neurotropic virus could not be demonstrated No neutralizing antibodies or nonspecific antivirus substances were found in cultures infected with the 17DD High strain of yellow fever virus

The diverse nature of the viruses between which interference is demonstrable indicates that a fundamental mechanism common to all systems studied is responsible for the phenomenon Formation of antibodies or nonspecific antivirus substances does not seem to be the cause The mechanism is undoubtedly associated with some interaction of virus and susceptible cells of the tissue culture

Interference between Bacterial Viruses Mutual Exclusion Effect and Depressor Effect M Delbruck (Vanderbilt Univ) defines the mutual exclusion effect as that which occurs when several viruses are introduced to a bacterium but only one virus will grow The depressor effect is that which is exerted by the virus which does not grow but which nevertheless reduces the yield of the growing virus Experiments concerning these phe

(2) J B t 50 151 170 A g t 1945

nomena were made with virus strains alpha and delta

Bacteria simultaneously infected with viruses alpha and delta were lysed after a time interval of 13-17 minutes which is the same time as that for unmixed infection by either virus Every bacterium infected with both viruses liberated either virus alpha or virus delta but never both this demonstrates the mutual exclusion effect at work For equal multiplicity of infection with both viruses about one third of the bacteria liberated virus alpha the rest virus delta A group of viruses which attack one host can be arranged in a series according to their exclusion power In mixed infections with alpha and delta the average yield of virus from the bacterium was much less than in unmixed infection The excluded virus depressed the yield of the successful virus This depressor action diminished gradually when the time between addition of the two viruses was increased There was a critical time interval beyond which there was no depressor action The length of this time interval depended on the nature of the first virus and was independent of the nature of the depressor virus

Antibacterial serum added in high concentration before the second virus prevented adsorption of the second virus If added in low concentration the antibacterial serum did not prevent adsorption but diminished the interfering action Antivirus serum added after adsorption of a virus diminished its depressor action

Delbruck set up a working penetration hypothesis which assumes that penetration of the first virus into the cell makes the cell membrane impermeable to any other virus that each virus has a characteristic time of penetration and that the change in permeability occurs at the end of this time interval uniformly for the entire cell membrane the dividing cells acting as a unit up to the moment of separation The depressor effect was interpreted as competition for a common substrate between the virus which penetrated into the cell and the excluded virus

Relationship between Virus of Infectious Ectromelia of Mice and Vaccinia Virus was studied by F M Burnet and W C Boake[3] (Melbourne) The virus of ectromelia of mice gives rise to a hemagglutinin closely resembling that produced by vaccinia virus Preparations of infected chorioallantois or mouse liver agglutinate only some bird cells cells which are agglutinable by vaccinia preparations are agglutinable by ectromelia material and cells inagglutinable by one are also inagglutinable by the other Neither virus acts on rat guinea pig calf or human cells but ectromelia virus preparations agglutinate mouse cells against which vaccinia preparations of equal or higher titer are inert Ectromelia hemagglutinin is completely absorbable by susceptible fowl cells but not by insusceptible cells The two types of cells produce equal small reductions in virus titer This indicates that as in vaccinia the virus itself is not the hemagglutinin Serums produced by immunization of calves rabbits mice and men against one or the other virus show specific inhibition of hemagglutination by both types of virus preparation the titers being usually higher against the homologous type Rabbits can be infected sometimes fatally by intravenous injection of ectromelia virus survivors are always immune to intradermal infection with vaccinia virus Mice inoculated intravenously with vaccinia virus develop antibody against both viruses and become resistant to at least 10^4 infective doses of ectromelia virus

These findings establish an unequivocal biologic relationship between the viruses of vaccinia and infectious ectromelia The immunologic resemblance is so close that it leads to the conclusion that the two viruses are ultimately derived from a common ancestral form The two viruses have also other common features Both are relatively robust forms which survive well in broth filtrates or glycerolated emulsions at ordinary refrigerator temperatures It is probable that the elementary particles

(3) J Im 1 53 1 13 M y 1946

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over large areas by killing both adults and larvae aerial applications of DDT can be very useful Through continuous and general use of residual sprays in buildings malaria may be controlled in most regions Since most anopheline mosquitoes alight on the walls or furniture before biting after feeding the insecticide can get in its deadly action before the insects become infective and transfer the disease to other persons

Flies—Deposits of DDT from an oil solution or a suspension applied at the rate of 100-200 mg DDT per sq ft to walls ceilings window sills light fixtures etc will continue to kill flies for two to eight months If flies are once markedly affected by contact with DDT they ultimately die Horseflies and deer flies which play a part in the transmission of tularemia and anthrax are rather resistant to DDT By spraying barns and other outbuildings with DDT contamination of dairy products by flies can be greatly reduced Emulsions of DDT in bay water have been found effective in controlling the breeding of stableflies in deposits of marine grasses Spraying slaughter houses fish meat and other food packing plants and market places with DDT greatly reduces food contamination DDT solutions are highly effective in destroying sandflies both Phlebotomus which carries kala azar verruga and sandfly fever and Culicoides which carries filarial worms Black flies or buffalo gnats are killed by contact with DDT sprays and the larvae are killed by introducing DDT emulsion into infested streams

Fleas—Fleas are destroyed by spraying infested rooms especially floor coverings and overstuffed furniture with a 5 per cent solution in odorless kerosene A 5 or 10 per cent DDT powder applied lightly to the back and neck of a dog will kill its fleas Cats lick themselves and may swallow the insecticide and die Oil solutions should not be applied to any animal because it may burn the skin or be absorbed

Bedbugs—DDT is superior to any other treatment of

of both viruses are of similar size If ectromelia is a member of the group of mammalian pox disease it is possible that some or all of the other viruses of the group are also producers of a similar hemagglutinin The authors stress the significance of hemagglutination as a possible index of species susceptible to the viruses concerned In the light of present knowledge the virus hemagglutinins may be divided into three groups I the influenza viruses Newcastle disease virus fowl plague II the pox viruses—vaccinia variola ectromelia of mice III the pneumonia virus of mice which acts on murine cells only

Present Position of DDT in Control of Insects of Medical Importance is reviewed by Fred C Bishopp[4] (Washington D C) DDT is not effective against all kinds of insects It acts as both a contact and stomach poison but is particularly effective as a contact killer Its effect on insects is not rapid its initial effect being to excite the insect After an insect shows marked symptoms of poisoning however it seldom recovers One of the outstanding characteristics of DDT is its persistence

Mosquitoes—DDT is a highly potent culicide As little as 1 part in 100 million parts of water is fatal to larvae of some species of mosquitoes The adults too are suscep tible as little as 1 gamma on the body will produce death It has little effect on the pupae however and no effect on eggs The larvae or wrigglers which are found only in water are extremely susceptible to DDT applied in oil solution emulsion or suspension Larvae of the malaria mosquitoes are much more easily killed than those of the pest mosquitoes especially of the genus Culex DDT ap pears to be 100 times as toxic as phenothiazine to larvae of Anopheles quadrimaculatus It has been shown that 1/10 lb DDT per acre almost completely destroys mos quito larvae when applied either as emulsion DDT 20 xylene 60 or Triton X 100 20 per cent or as a 5 per cent solution in oil In cutting down mosquito population

(4) Am. J P b H alth 36 593 606 J 1946

Laboratory Procedures for Brucella I H Borts[5] (Iowa City) states that the blood culture is most important in diagnosis of brucellosis because all other tests particularly the skin test may give positive or negative results in absence or presence of the disease The blood culture is usually positive when made early in the disease and at the height of fever when made later and during the chronic stage it may be negative Certain technical factors must be considered when making blood cultures

TECHNIC —After receipt of the blood culture bottle the culture is incubated for 24 hours after which the rubber stopper is replaced with a sterile cotton plug and the culture is again incubated under 10 per cent carbon dioxide Then 0 5 cc of the thoroughly mixed culture is removed with a sterile capillary pipet and transferred to a tryptose agar slant. The transfer is incubated under 10 per cent carbon dioxide for 72 hours and then examined If growth is present a Gram stain is made and the staining reactions and morphology are noted Two fresh slants are inoculated one being incubated under 10 per cent carbon dioxide and the other under ordinary atmospheric conditions at 37 5 C and the growths compared daily for 72 hours A liver infusion agar slant is inoculated and a sterile strip of blotting paper treated with 10 per cent solution of lead acetate is placed in the tube so that the paper does not touch but extends down about 1 in below the upper edge of the inoculated medium This slant is incubated under 10 per cent carbon dioxide for 24 hours and the degree of hydrogen sulfide recorded. A fresh lead acetate-treated paper strip is replaced daily for four days The growth on the original and on subsequent slants is tested for agglutinability against known antibrucella serum A loopful of a concentrated saline suspension of the organism is inoculated onto two dye slants one tryptose agar slant pH 6 6 containing basic fuch in in 1 25 000 dilution and another containing thionine of the same dilution and incubated 72 hours under 10 per cent carbon dioxide and the growth noted Blood cultures are subcultured semiweekly for 21 days before being discarded as negative Growth is frequently noted on the first subculture but cultures containing Brucella abortus are rarely positive that early This type usually requires 1[n]

(5) Lab D g 9 1 3 M b 1946

bedbugs It is not so dangerous as hydrocyanic acid gas fumigation and has the advantage over pyrethrum and other sprays of being persistent Sprayed on mattresses and bedsteads it will continue to kill bedbugs for months There is reason to believe that DDT residual sprays will be of great value in destroying kissing bugs (Triatoma) which transmit Chagas disease to man

Lice —The efficacy against body head and crab lice of 10 per cent DDT in pyrophyllite has been fully demonstrated by the Army The protection of troops and civilians from louse infestation has shown its value in preventing typhus Impregnation of clothing by dipping in a DDT emulsion or solution and leaving DDT in the garments to the extent of about 2 per cent of their weight gives protection against lice for several weeks

Ticks —DDT dusts emulsions and solutions are valuable in combating ticks such as the American dog tick the lone star tick ticks on horses and the brown dog tick

Mites —In general DDT is not very effective against mites Plant feeding forms such as the European red mite and the common red spider often multiply rapidly after trees are sprayed with DDT Parasitic mites on rats are not satisfactorily controlled Some tests with DDT on chicken mites gave favorable results others did not A formula which has been found effective against human scabies and lice consists of benzyl benzoate 68 ethyl p aminobenzoate 12 sorbitan mono oleate polyoxyalkylene ether derivative 14 and DDT 6 per cent This material diluted 1 part to 5 parts of water is applied to the entire body

suggested that booster or activating doses of toxoid be given to all age groups of the present population The Minnesota Department of Health recommends that all children immunized early in childhood should receive booster doses of toxoid before they enter school

Diphtheria Carriers Treated with Penicillin are reported on by Rudolph A Kocher[7] (Carmel Calif) and Walter J Siemsen (Denver) Nine patients who had recovered from clinical diphtheria and continued to show positive cultures for two to seven weeks after symptoms had subsided were given intramuscular injections of 25 000 units of penicillin every two hours for seven days a total of 2 100 000 units Cultures remained positive in all This can be explained by the fact that the diphtheria organism has little capacity to invade the body and is found almost exclusively on the surface of the affected mucous membranes Its effects are due entirely to the soluble toxin absorbed from the surface of the mucous membranes

Thirty one diphtheria carriers were treated with glycerin and gelatin penicillin lozenges that required 20–30 minutes to dissolve thus giving prolonged contact with the throat by the released penicillin Lozenges contained 500 and 1 000 units Each patient received one every hour for 12 doses during waking hours for 3–5 days In addition nasal penicillin sprays containing 1 000 units per cc were given every two hours during the same period Five consecutive daily negative cultures were obtained in 23 patients The eight patients who did not respond to this treatment alone had negative cultures after tonsillectomy without further penicillin treatment with one exception in this patient cultures became negative when he was again treated with the lozenges and spray That cultures became negative in seven patients only after tonsillectomy indicates that the tonsils are important sites for harboring diphtheria bacilli That the nasal passages also may serve as a focus was shown

(7) Ann Int Med 24 883 886 May 1946

per cent carbon dioxide for growth and produces hydrogen sulfide in moderate amounts for two successive days and then declines It grows on tryptose agar containing basic fuchsin and is inhibited in presence of thionine Brucella suis does not require carbon dioxide it produces hydrogen sulfide in large amounts for four successive days and then declines It grows on tryptose agar containing thionine and is inhibited in presence of basic fuchsin Brucella melitensis does not require carbon dioxide Most Iowa strains grow better on solid mediums under ordinary atmospheric conditions It produces *no or little hydrogen sulfide and grows equally well on* the two slants

Diphtheria Report of Six Deaths Harold H Joffe and Arthur H Wells[6] (St Luke s Hosp Duluth) point out the seriousness of the problem of diphtheria as evidenced by the outbreak of several epidemics in various parts of the world since the beginning of the last war and the severity of the malignant type of diphtheria which requires immediate proper therapy to prevent death

Certain characteristic clinical phenomena occur in the malignant type which aid in recognition of the disease and institution of proper and prompt therapy Onset is sudden and severe and there is frequently an associated cervical cellulitis which gives rise to the bull neck appearance and must not be confused with mumps Respiration is of the snoring type because of intense swelling of the pharyngeal parts Thick membrane covers tonsils anterior pillars and uvula and may extend to the mucous membrane of the hard palate and cheeks The tonsils may be so swollen as to compress the uvula The membranes are gray or even darker because of hemorrhage following necrosis of the underlying tissue with development of gangrenous areas Involvement of the nasal mucous membrane with nasolabial excoriations is common The temperature is generally very high and the fever runs a septic course Evidence of circulatory failure appears early

Because of the present increase in diphtheria it is

(6) Minnesota Med. 9 335 339 Ap 1 1946

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(7) A I t M d 24 883 886 M y 1946

by one patient in whom nasal cultures remained positive after tonsillectomy and by another in whom cultures became negative only after nasal spray was added to lozenges

Contagiousness of Leprosy T Canaan[8] (Jerusalem) recounts his experiences at the Jesus Hilf Leprosarium Undoubtedly leprosy is contagious but the manner in which Mycobacterium leprae is spread is still not definitely known Several factors appear to be necessary for contraction of the disease among them close and *prolonged contact with lepers continuous dissemination* of the bacilli youth poor constitutional health and lack of a natural or acquired immunity However it is still surprising how few persons contract the disease despite close association with lepers None of the nurses working in the Leprosarium in some instances over 30 years contracted the disease nor did four patients with other diseases who were in this institution from 12 to 47 years and who lived in close daily contact with lepers Natural immunity strengthened by acquired immunity and decrease in virulence of the specific bacillus apparently are responsible for this low incidence of infection The attenuation of the bacillus is evident among other things from the fact that the disease is progressively decreasing especially among the Arabs The number of cases of leprosy in Palestine decreased in the last 75 years from 220–250 to 120–150

Isolation of Mycobacterium Leprae in Culture is reported by R Row[9] A weak saline suspension of Mycobacterium leprae was made from the material of leproma of a patient with cutaneous leprosy and a few cubic centimeters of this weak suspension was planted into a tube of hemoglobinized saline after allowing four days to obviate extraneous contamination the tube was infected with one drop of a leishmania culture 10 days old and was left to incubate at 20 C When examined

(8) Acta med. orient. 4 181 184 June 1945
(9) Ind m J h sci n 5 75 81 April 1946

a week later in a fresh drop it showed many active flagellates and many rosettes of these in different sizes After drying and staining with the Ziehl Neelsen technic the drop presented a marked proliferation of acid fast bacilli in close contact and inside leishmanial rosettes individually the bacilli were fatter and longer than those seen in smears of the original lesions

The growth in the fluid medium was then transferred to solid mediums (1) on the surface of the solidified hemoglobinized saline agar to obtain a symbiotic culture on a solid surface at 20 C (2) on the surface of a glycerinated potato to isolate the acid fast bacilli at 37 C and free them from leishmania which cannot grow on this medium and at this temperature After 10-15 days incubation the symbiotic culture showed a translucent film consisting mainly of leishmania but the film was interspersed with many fine yellow colonies which when examined microscopically after staining with the Ziehl Neelsen technic were found to be acid fast bacilli shorter than those in the parent symbiotic culture These colonies planted on solid glycerinated agar and on glycerinated potato at 37 C yielded in two weeks pure cultures made up of coccic forms and some coccobacillary intermediaries but all acid fast The original potato culture also presented a distinct yellow film after two weeks this film thickened and at the end of four weeks presented distinct tubercle like masses heaped up on the surface Microscopically the culture was made up of fine uniform cocci like staphylococci or streptococci but all acid fast Subcultures were easily made from this parent culture

Observations show that in symbiosis the leishmania aids the helpless parasite to grow by sharing the split products of the nutrient material and enables the weaker organism to grow on its own independent from further support

Mycobacterium stefanski which causes rat leprosy and which like Mycobacterium leprae is unculturable

in the ordinary way could be cultured by the same method

[A number of methods of cultivating Mycobacterium leprae have been reported which have not been successful in the experience of others The method described here needs confirmation — Ed]

Melioidosis Charles D Cox and J L Arbogast[1] report the first case of Whitmore s disease in the Army of the United States

American Indian soldier 27 complained of fever of 24 hours duration together with headache chills nausea vomiting and pains in the chest lower back and joints of the legs During 21 months overseas he had had three attacks of malaria He had been in Assam and in Burma He had previously been a mule skinner and some of his mules had died of illness Examination revealed a palpable liver and spleen Parasites could not be demonstrated During the next few days scattered pustules appeared over the entire body and some of them went on to the crusting stage Moderate abdominal distention developed On the fifth day he became irrational and there were signs of pneumonic consolidation At first smallpox then staphylococcic septicemia was suspected Penicillin was given but the patient died after having had a temperature of 104 F and a pulse of over 160 Cultures made of both blood and skin pustules on the fourth hospital day had shown a gram negative motile bacillus after two days growth This bacillus was also grown during postmortem studies and was identified as Malleomyces pseudomallei the agent responsible for melioidosis When a broth culture of this bacillus was injected into a guinea pig a fatal septicemia developed in 48 hours

The authors emphasize the salient characteristics of the bacillus because more cases may be expected in soldiers stationed in the Far East These include (1) marked bipolar staining (2) active motility (3) rapid profuse growth on laboratory mediums and colony characteristics on 5 per cent glycerin agar (4) fermentation of many of the carbohydrates in 72 hours with production of acid but not gas (5) ability to grow on McConkey s agar and inability to grow on Bacto S S agar (6) rapid liquefaction of gelatin and (7) production of a positive Strauss reaction in the guinea pig

(1) Am. J Cl i. P th 15 567 570 Dec mbe 1945

Diagnosis of the disease depends entirely on the bacteriologic identification of the bacillus

Melioidosis on Guam George S Mirick Harry M Zimmerman George D Maner and Arthur A Humphrey (M C U S N R) report two cases observed on Guam in both of which diagnosis was made by postmortem examination and by isolation of Pfeifferella whitmori The disease usually appears as an acute or subacute septicemia with death in three days to four weeks In human beings it is believed to be contracted by ingestion of infected food or water In these cases infection reservoir probably was one or both of two rat species (Rattus rattus and Rattus exulans) which inhabit the island

The organism isolated in the first case grew readily under aerobic conditions on all usual culture mediums including Koser s citrate medium On nutrient agar containing 6 per cent human blood the colonies were round low convex translucent and grayish The freshly isolated strain produced slight hemolysis after growth for 24 hours at 37 C a phenomenon not appearing on subculture After growth for three days the colonies became grayish yellow Growth for three days on tryptose phosphate agar produced a characteristic rough phase The bacterium grew well in broth with formation of a pellicle It was an actively motile pleomorphic rod gram negative with characteristic bipolar staining A small amount of acid but no gas was formed with glucose and galactose in two days with lactose mannitol xylose maltose sorbitol and adonitol in six days and with sucrose in nine days Rhamnose dulcitol and trehalose were not acidified in 10 days Gelatin showed stratified liquefaction of about 1 cm below the surface after three days at 22 C Methyl red test and tests for formation of hydrogen sulfide and indole were negative Ammonia was produced from peptone Nitrates were reduced actively to nitrites Methylene blue was reduced and catalase was produced

(2) J A M A 130 1063 1067 Ap 20 1946

milder prevalences it has been causally related to the outbreak but not present in most cases selected for study, still other outbreaks of influenza have been shown to be made up of interspersed cases of influenza A and influenza B In addition most observers have noted occasional instances of serologic responses to virus of both types, although no other evidence of simultaneous double infection is at hand The variations in distribution of influenza B have extended therefore, from nationwide outbreaks of moderate severity to those resembling a mild endemic disease

No sharp clinical and epidemiologic differentiation between the diseases is available nor has any well defined difference in the pathologic changes induced by the two types of virus been recorded Immunologically however, they are quite distinct. Infection with one elicits neither specific antibodies nor immunity to the other repeated inoculations fail to induce cross reactions between them The antigen which reacts in the complement fixation test while common to dissimilar strains of the same type does not react with serum of heterologous type From the point of view of immunity therefore the two diseases must be considered independent factors in the epidemiology of influenza

Despite strain and type differences the characteristics of the disease remain so similar that the agents may be considered a pathogenic unit Infection is induced via the respiratory tract where after 24 to 48 hours the epithelium of the respiratory passages is selectively attacked and destroyed following which the extensive pneumonia of the fully adapted experimental disease develops

The animal which recovers from the virus disease develops circulating antibodies to the virus and an immunity which persists for months and then wanes to leave modified resistance In this stage the animal responds to reinoculation with fever and nasal signs and

the respiratory epithelium is again destroyed but the typical pulmonary lesions do not develop Animals which have been repeatedly inoculated develop a broader resistance which persists for a longer period and which serologically is effective against more divergent strains There is reason to believe that the susceptible tissue is also modified so as to be more resistant to virus attack under which condition dependence on antibodies would decrease The human subject responds to infection with development of circulating antibodies and presumably with immunity Duration of immunity in man is not known but presumptive evidence indicates that an acquired resistance exists for a year or two at least Nevertheless the fact that many individuals possess antibodies to virus of type A and that a large proportion of those who become ill have circulating antibodies when they become infected is a clear indication that antibodies acquired through previous infection with virus of the same type do not bestow prolonged immunity However in general the antibody titers of patients in the acute stage of illness are lower than that of the average individual who does not become ill and the natural suggestion is that resistance is proportionate to antibody level

Control efforts have centered on development of a satisfactory vaccine for subcutaneous administration Although resistance can be produced in animals and antibodies induced in man by a variety of preparations evidence of the protection of man against the natural disease is inconclusive There are nevertheless suggestions that the severity of the disease may be reduced and the complications limited Even if it should be true there also exists the problem of variations in the virus and the possible necessity of incorporating in the vaccine virus similar in composition to the one in circulation For this reason it is necessary to be alert for the earliest evidence of the nature of an outbreak If the

virus could be isolated quickly its introduction into a *vaccine would not be difficult but the time relations are* extremely important

In addition to subcutaneous vaccination possibility of passive immunization by use of serum intranasally is being explored For this purpose serum can be collected beforehand or obtained from convalescents early in the epidemic period and used on other exposed susceptibles Intranasal vaccination with virus offers another approach

A different concept of control is presented in the form of physical or chemical barriers which serve to prevent transfer of infectious material Of these the aerosols offer the greatest promise because of simplicity of application and adaptability to a wide variety of conditions under which crowding and air contamination are extensive The efficacy of sulfonamide compounds furnishes great confidence that the serious bacterial complications will be susceptible to treatment and that attendant mor*tality can be greatly reduced*

[The two preceding articles are excellent expositions and give us some understanding of the difficulties of the influenza problem. —Ed]

Inactivation of Influenza Viruses by the Human Skin[1] The personnel of Naval Laboratory Research Unit No 1 (U S N R Univ of California) tested type A influenza virus for its ability to withstand desiccation on the human skin on glass surfaces and on strips of cellophane adherent to the skin Similar tests were con*ducted with type B* virus using in addition virus suspension dried on thin rubber sheeting attached to the skin Both types were completely lacking in capacity to infect mice after 10 minutes in the dried state on human skin The type A controls dried on glass and on cellophane for 40 minutes showed no drop in virus activity while type B controls dried on glass cellophane or rubber sheeting lost their infectiousness nearly as rapidly as the skin dried virus The authors conclude that man

(1) U S N M B U 40 839 846 Octobe 194

ual transmission of dried influenza viruses is not apt to be an important hazard in spreading the disease

Acute Febrile Illness with Rash and Leukopenia Due to Haemophilus Para-Influenzae is reported by Alfred E Florman[2] (Mount Sinai Hosp New York City)

Boy 7½ was admitted with fever and rash He had never had measles scarlet fever or diphtheria Diphtheria toxoid had been administered 10 days before admission Illness began six days later as a mild upper respiratory infection and the following day he had chills and temperature of 104 to 105 F with inflamed throat and obstructed nasal passages The next day he became drowsy The morning of admission the mother noted a number of small red spots in the axillae and behind the ears Twelve hours later the eruption covered most of the body and a peculiar enanthem was noted For several hours preceding admission he complained of a slight frontal headache His parents considered him more drowsy and the physician though there might be a meningeal infection despite absence of vomiting convulsions and neck pain There was no recent exposure to infectious disease and the only drug given before admission was aspirin There was no family history of allergy

The boy was drowsy and acutely ill on admission Temperature was 101 F, pulse 118 and respirations 24 Scattered over the body were many small pinpoint and pinhead sized purpuric spots, most abundant in the axillae popliteal areas and at pressure points and infrequent on the head hands and feet Mucous membranes of both lower lids were engorged There was bilateral mild catarrhal otitis media nasal mucosa was red and edematous and there was a thick yellowish purulent exudate in the left nostril The palatal mucosae were beefy red and presented small whitish papules simulating early Koplik spots with a few similar lesions on a beefy red base on the upper gums Buccal membranes were relatively clear Uvula and tonsils were red and edematous with a few yellow gray follicles on the left tonsil a diffuse purulent postnasal drip was noted Fetor was present Cervical and inguinal lymph nodes were palpable Heart and lungs were essentially normal Abdomen was soft liver and spleen were not palpated Except for the eruption the extremities were normal The neck was supple Kernig's Brudzinski s and Babinski s reflexes were negative Deep tendon reflexes were hypoactive Despite drowsiness he was co operative and would follow a

(2) J P di t 0 34 F b y 1943

light There was no gross facial weakness and there was no weakness of the extremities Nystagmus was also absent

Blood studies revealed 70 per cent hemoglobin, 4,200,000 erythrocytes 6 800 leukocytes, with 37 per cent adult poly morphonuclears, 9 per cent juvenile polymorphonuclears, 1 per cent myelocytes 5 per cent eosinophils 44 per cent lym phocytes and 4 per cent monocytes Bone marrow and urine were normal Cerebrospinal fluid was clear and contained 60-80 erythrocytes and 3 leukocytes per cu mm Pandy's re action was negative. Pressure could not be evaluated Culture of the cerebrospinal fluid yielded para influenza organisms Blood culture was sterile Throat culture yielded a beta hemo lytic streptococcus Tonsillar smears contained a few spiro-chetes and fusiform bacilli Heterophile agglutination was positive only to 1 16 Serum obtained 10 days before admis sion agglutinated a suspension of Haemophilus para influenzae in a dilution of 1 80 Patch tuberculin, Schick and Wasser mann tests were negative

He was given 60 cc of 1 per cent sodium sulfadiazine intravenously and 0.5 Gm sulfathiazole every six hours by mouth Chemotherapy was continued for three days during which the temperature gradually fell to normal Five days after admission the rash had completely faded the throat was only slightly reddened and only a few residual lesions remained Leukocyte count remained between 5 000 and 10 000 Sensorium cleared rapidly and he was discharged the eleventh day One month later serum failed to agglutinate his particu lar strain of Haemophilus para influenzae

In most Haemophilus influenzae infections rashes do not play a prominent role Florman found no descrip tion of an enanthem similar to that seen in this child. *The hemorrhagic eruption particularly in pharynx and* mouth, was so impressive that it may be possible to sus pect para influenza infection in similar cases The leukopenia is also unusual Haemophilus influenzae usu ally causes leukocytosis

MALARIA

Malaria As a World Menace is discussed by L T Coggeshall[3] (Univ of Michigan) Accurate figures on the morbidity and mortality of malaria are not available but there is ample evidence that it is one of the greatest medical problems of our time Surveys indicate that in many countries the rate of infection is 100 per cent of the population In the United States it is probable that there are a million cases annually resulting in 5 000 deaths

All the conditions which enable malaria to maintain this position are present during wars and in addition a new group of epidemiologic factors appear which greatly accelerate its acquisition and dissemination The location of troops is the most important factor A major proportion of American troops overseas is in tropical areas in close contact with huge native malarial reservoirs If the proposed figure of 11 000 000 men in the armed services is ever approached which means practically one half of the adult American male population and if the same proportions are to serve in the tropics as now then some appreciation of the probable consequences can be gained The men will be located in Africa the Middle East China and the Southwest Pacific where a major percentage of the civilian population is affected with malaria For example in Liberia 90 per cent of children under 5 have positive blood smears most of them harboring the gametocytes necessary to infect mosquitoes and 70 per cent of adults are continuously infected These adults represent the survivors who have developed a tolerance for the disease as they are in apparent good health yet maintain an intensity of infection that would incapacitate the white man The rates cited for Liberia are not excessive for most of the other tropical areas Efficient vectors are also present in excessive numbers

(3) J A M A 122 8 11 M y 1 1943

The most dreaded vector of all, Anopheles gambiae, is particularly prevalent in Africa. In India there are probably 12 suitable species of vectors The combination of infected reservoirs, accessible efficient vectors, climatic conditions favorable for year round transmission and a ready supply of susceptible hosts can only result in a high incidence of malaria in the army

Medical officers are making serious efforts to curb the infection Malarial survey and control units are being sent to the battle areas where the problem is most acute Control measures will largely be limited to the use of nets insecticides sprays and suppressive drugs Despite the most efficient application of such measures it will be difficult to diminish the incidence appreciably Deficiencies exist in prophylaxis and treatment Only atabrine is available for suppressive effects of the clinical symptoms as limited quinine supplies must be used for treatment Atabrine does not prevent inception of malaria only its acute manifestations It is not a perfect suppressive drug and quinine likewise is only partially effective in this respect

When used therapeutically neither atabrine nor quinine will eradicate an infection They merely control an acute attack and if an individual succeeds in throwing off the infection it is by the effort of his own defensive mechanism

The return of infected troops to hospitable territory is likely to result in serious epidemics especially where control efforts are lax because of the absence or low incidence of malaria Serious outbreaks can be expected if for no other reason than the increased number of infected persons. But in addition throughout the United States there is an abundance of Anopheles quadrimaculatus the important mosquito vector for this country It thrives as far north as the Canadian border and will transmit any of the three human plasmodia. There is also danger that new vectors may be introduced

It has been suggested that it is unlikely that malaria

can cause much trouble in this country since the disease is already indigenous particularly in the South. Unfortunately the tolerance a population develops against a strain of malaria by virtue of repeated infections confers little immunity against strains from other areas It is possible for an individual to have the three human malarial infections in the same year or subsequent attacks produced by different strains of the same species Thus the mass rehabilitation of sick troops allows for the establishment of epidemics over long periods even in malarious areas and there is no means of halting the spread by immunization procedures

Widespread recognition of the danger can result in more effective control effort The stimulus will come from secondary outbreaks traceable to imported infections At the first sign of such episodes an all out effort should be instituted by local state and federal authorities If this is done early the danger of spread can be averted

Malaria in Wartime P H Manson Bahr[4] discusses the two malarial parasites most important in military medicine which cause fever differing considerably in clinical appearance and in treatment

Benign tertian malaria is caused by Plasmodium vivax The cycle of parasitic activity in the erythrocytes recurs every 48 hours at the end of which the malarial rigor or fever occurs Coincident with development of the sporulating form there occurs within the erythrocyte substance a degeneration of the protoplasm known as Schuffner s dots peculiar to the benign tertian and ovale parasites alone In contradistinction to subtertian malaria multiple infections of the corpuscle by more than one parasite are rare in benign tertian malaria

The classic features of a malarial attack are the cold hot and sweating stages the last occurring when temperature begins to fall Rigors recur on alternate days in benign tertian malaria at exactly the same time with

(4) B t M J 2 461-46 O t 17 489-491 Oct. 24 1942

explosive suddenness Temperature may be 104 106 F, falls abruptly and afterwards becomes subnormal. Classic tertian periodicity is not always observed in benign tertian malaria Particularly in primary infections atypical fevers resembling tuberculosis or typhoid fever may be expected Formerly quotidian rigors were mistakenly attributed to two generations of parasites running concurrently rather they are due to response of the body to a primary infection for typical tertian periodicity is not attained until the fever has lasted for several weeks

Subtertian malaria caused by Plasmodium falciparum differs from the benign tertian disease in its protean manifestations and greater malignancy Plasmodium falciparum does not enlarge the parasitized erythrocyte and the infected corpuscles tend to agglomerate so that development mostly proceeds in the capillaries of internal organs Because of this the parasite does not freely circulate in the peripheral blood as does the benign tertian Likewise peripheral blood smears do not reveal the complete developmental cycle for some stages develop in the sinuses of the spleen pancreas brain intestinal capillaries and other viscera. The clinical appearances of the fever depend on the organ in which maximal multiplication occurs.

Blood films disclose the subtertian parasite initially to resemble a flattened signet ring and subsequently to be plastered to the edge of the corpuscle multiple infections of the cell are common Irregularity in corpuscular outline is observed and protoplasmic staining properties vary The sporulating stage occurs almost entirely in the internal capillaries the affected corpuscles agglutinate forming thrombi in which the sporulating form develops With the sporulating stage prognosis is grave

The blood film of fatal cases reveals rapid multiplication of the parasite in the erythrocyte the two bifid

nodules of chromatin which usually indicate severe infection and large hyaline mononuclear cells containing ingested parasites The subtertian parasite does not produce Schuffner s dots in the erythrocyte protoplasm, but forms distinctive fissures or holes (Maurer s dots or clefts)

The fever of subtertian malaria usually has quotidian periodicity but almost any variety of temperature may be produced Occasionally a sudden drop in temperature is followed by an immediate rise The temperature curve with double rises of temperature with dicrotic notching is limited to benign tertian malaria Subtertian malaria may lie dormant producing no fever until lowered resistance initiates symptomatic onset

Malaria produces splenomegaly and splenic pain Malaria may simulate almost any other disease subtertian is the greatest mimic Often it produces cerebral symptoms owing to the congregation of parasites in the brain sometimes leading to coma and death Such attacks may be confused with heat stroke alcoholism mania epilepsy and cerebrospinal meningitis. It may also simulate appendicitis cholecystitis or colitis The most dramatic sequel is blackwater fever solely associated with subtertian malaria Blackwater fever is apparently the result of supersaturation with the subtertian parasite and therefore seldom occurs after a primary infection It occurs mostly in persons who after long residence in the Tropics return to temperate regions and are exposed to cold dampness or shock which causes sudden multiplication of parasites The erythrocytes then break down and become hemolyzed and the patient may die from blocking of the kidneys with the products of such disintegration Treatment depends on alkalinization of the blood and prompt blood transfusions

Arms and Anophelines or the Military Significance of Malaria Robert Fowler[5] (M C R A A) describes

(5) M J Aust ii 2 455-459 Nov 21 194

the military significance of malaria in Asia Minor particularly as it influenced Allenby's campaign in Palestine Syria and Transjordania

Symptomatology of Malaria P H Birks[6] describes cases observed in a military unit which suggest that the malarial parasite can exist in the peripheral blood and produce diverse pathologic conditions without pyrexia These include back pain rheumatic joint pain swelling and pain in the testicles urticaria multiple conjunctival ecchymosis, cardiac irregularity recurrent diarrhea and obstinate eczematoid conditions without fever In the 11 cases reported either the malignant tertian or benign tertian parasite was found in thick blood smears All patients responded to antimalarial treatment after the usual symptomatic treatment had failed Birks concludes that malaria in this form is due to the effects of the disease on the arterioles and capillaries

Treatment of Malaria The principal drugs used are quinine and atabrine Heroic doses of quinine are now recognized as useless and similarly dosage so administered as to catch the sporulating form of the parasite has been discarded The objective sought in treatment at present is to insure a sufficiency of quinine in the blood throughout the period of treatment The maximal dose of quinine now used in acute malaria is 2 Gm per day and many consider 1 3 Gm to be adequate Prolonged administration of quinine is useless seven days treatment is adequate to combat the attack Prophylactically quinine is used by either of two common methods (1) 0 32 0 45 Gm daily or (2) 1 Gm on two successive days in the week

In general similar usage may be made of atabrine This may be given in three daily doses of 0 1 Gm each *The toxicity of atabrine is not great* but gastro-intestinal and nervous reactions may occur The cumulative effect of atabrine necessitates care in its administration

(6) Brit M J 1 784 785 J 6 1943
(7) J A M A 1 0 335 Oct 3 194 Foreign letter

In acute attacks it is usually not given for more than seven days if necessary it may be repeated after a rest interval Atabrine must also be used cautiously in prophylaxis 0 2 Gm on two successive days in the week or even at longer intervals is recommended

Atabrine has an advantage over quinine in its suitability for intramuscular injection Ordinarily it is best given orally but when cerebral or other pernicious manifestations ensue its parenteral administration is indicated Quinine in such instances must be used by careful intravenous administration Intramuscular use of quinine is unjustified as absorption is too slow and necrosis with sloughing may occur

The Critical Antimalarial Problem and Its Solution Lewis H Weed[8] states that necessity for conservation of limited quinine stocks has caused recourse in malaria therapy to use of totaquine atabrine and plasmochin Totaquine is a mixture of alkaloids from the bark of Cinchona succirubra Pavon and other suitable species of cinchona (U S P XII) It contains not less than 7 or more than 12 per cent of anhydrous quinine and not less than 70 or more than 80 per cent of the anhydrous crystallizable cinchona alkaloids (cinchonidine cinchonine quinidine and quinine) In dosage of 10 gr three times a day for seven days totaquine should be as effective as quinine sulfate in oral treatment

Atabrine is also an effective antimalarial and in some ways is superior to quinine It has slower action and therefore is not as useful in initial treatment but after one to three days of quinine therapy atabrine is exceedingly effective The National Research Council has accordingly formulated the following therapeutic regimen

1 *Combined Q A P treatment* (method of choice)
   a) Totaquine or quinine sulfate 0 64 Gm (10 gr) 3 times daily after meals for 2 or 3 days or until pyrexia is controlled Then
   b) Atabrine 0 1 Gm (1½ gr) 3 times daily after meal for 5 days Then after 2 days without medication

(8) J A M A 1 0 1043 1044 N 8 194

c) Plasmochin 0 01 Gm 3 times daily after meals for 5 days except for the debilitated patient, who should receive only 2 doses daily (Discontinue if toxic symptoms occur Never give atabrine and plasmochin con currently)

2 *Atabrine plasmochin treatment* (for simple vivax, and other infections when no totaquine or quinine is avail able) Atabrine as in 1b for 7 days After 2 days with out medication, plasmochin 0 01 Gm. 3 times daily for 5 days, as in 1c

3 *Totaquine or quinine plasmochin treatment* (when no atabrine is available) Totaquine or quinine sulfate, as above for 7 days, during the last 5 of which accompany each dose with plasmochin 0 01 Gm 3 times daily

4 *Suppressive treatment* Atabrine 0 1 Gm (1½ gr) twice daily after meals on 2 days a week, allowing a 2-3 day interval between days of medication

Surveys indicate that barks from South America of low quinine content but sufficiently rich in total crystallizable alkaloids to make totaquine of U S P stand ards will be found in sufficient quantity to supply civil ian quinine requirements

Preliminary Report on Treatment and Prophylaxis of Malaria in Southeast Asia A H Hamilton[9] states that much quinine is wasted by use of too large doses and by protracted treatment courses requiring use of 500 to 680 gr quinine per course Accordingly Hamil ton presents the de Langen method which utilizes less quinine but has given excellent results in the Nether lands Indies

METHOD —Fifteen gr quinine hydrochloride (equivalent to 20 gr quinine sulfate) is given daily divided in two doses, for one week after onset of the attack Quinine therapy is then stopped pending appearance of a relapse which is then treated in the same way as the initial attack. This requires a total of 105 gr quinine during each attack

With this method two or three relapses may be ex pected in the case of tertian malaria one or two in quartan and usually none in subtertian malaria Tertian malaria therefore requires about 420 gr quinine admin

(9) U S Nav M. Bull. 41 267 72 J nu ry 1943

istered over 12 to 18 months while in subtertian malaria a single course of 105 gr usually suffices Quartan malaria is relatively rare in the Netherlands Indies and is therefore not considered. The de Langen method accordingly effects an average saving over the Standard Method of about 260 gr quinine for each case of tertian malaria and of some 550 gr in cases of subtertian malaria treated in the early stages Use of quinine hydrochloride rather than the sulfate or bisulfate is advocated because of fewer secondary effects and greater absorption

Quinine prophylaxis based on the 6 12 day incubation period of malaria consists of administration on two consecutive days of every week of 10 gr quinine hydrochloride at bedtime This so-called screening method attacks the parasite at its most vulnerable stage In contrast to prophylactic methods which use daily administration of quinine this method not only saves quinine but prevents development of tolerance to quinine which would make treatment of a malarial attack more difficult.

Estivo Autumnal Malaria with Frontal Lobe Syndrome Norman Q Brill and Victor L Pellicano[1] (M C A U S) describe a case of cerebral malaria in which aphasia alexia agraphia memory defect and confusion were associated with pyramidal tract involvement and bilateral forced grasp reflexes and organic psychosis Cure was effected by early administration of atabrine

Tertian Fever From the mouth of the Amazon to the Uruguayan coast the anopheles abounds Anopheles albitarsis and argyritarsis are bearers of benign malignant tertian and quartan fevers Both are most prevalent along the Brazilian coast during August

N J Zurutuza (Buenos Aires) reports three cases of tertian fever contracted on shipboard The first patient had such pronounced cyanosis that he was actually

(1) J A. M A 1 1 1150 1152 Ap 3 1943
(2) S m méd 49 448 449 Aug 0 1942

"blue," besides having dyspnea and a filiform pulse Parasitosis was intense He died in a few hours The second patient had hemorrhagic jaundice and acute dysentery which caused death on the third day Diagnosis was made from a blood smear The third a sailor who traveled between Buenos Aires and Rio de Janeiro, had intense anemia and splenomegaly, which had been diagnosed medullar aplasia He had been treated for a month unsuccessfully at home with liver extract iron and tonics Eight days after landing he complained of chills pallor and splenomegaly Neosalvarsan cured him

Zurutuza stresses the importance of correct differential diagnosis in these cases which are frequently not thought of because of their rarity

Influence of Biotin on Susceptibility to Malaria William Trager[3] (Rockefeller Inst for Med Research) has found that biotin deficient chickens and ducks developed much more severe infections with Plasmodium lophurae than did nondeficient control animals While a mild degree of biotin deficiency sufficed to increase susceptibility, even an extreme degree of pantothenic acid deficiency had no effect Biotin deficiency also increased the susceptibility of ducks to Plasmodium cathemerium In animals infected with Plasmodium lophurae the concentration of biotin in the plasma as well as in the red cells rose during the course of infection reached a peak at about the same time as the parasite number reached its peak and then returned to normal as the infection subsided While administration of additional biotin to animals partially deficient in biotin could be considered a specific measure tending to lessen the severity of infection with Plasmodium lophurae injection of biotin into animals fed a diet adequate in this vitamin had no antimalarial effects perhaps because the excess biotin was rapidly removed from the blood

(3) J Exper Med 77 557 562 Jan 1943

MEASLES

Studies in Measles Joseph Stokes Jr Morris Shaffer Geoffrey Rake Gerald O Neil and Elizabeth P Maris[4] (Univ of Pennsylvania) grew the virus of measles successfully on chick chorio-allantois and made as many as 40 successful passages Success of passage from embryo to embryo was determined by inoculation of monkeys the inoculations from various passages producing measles of varying severity Measles thus produced was similar in all respects to measles produced by injecting blood or nasopharyngeal secretion from active cases with similar marked variation in signs and symptoms All monkeys inoculated with this type of active virus were immune when later injected with challenge inoculations of blood or nasopharyngeal secretion from active cases

Children were inoculated intranasally intradermally subcutaneously and by a finely divided and inhaled spray of the virus from various passages Development of measles in monkeys inoculated simultaneously with the same material confirmed presence of active virus in the children s inoculates Great variation was observed from signs and symptoms indicating mild measles (Koplik spots slight fever mild rash rhinitis conjunctivitis and slight cough) in some children to no signs and symptoms or slight rhinitis in others When possible challenge inoculations of blood from patients with active cases of measles at suitable intervals and by various routes followed original inoculation of the child with the chorio allantois virus Several children were also exposed to active measles Results suggest that immunization can be obtained in children similar to that produced by the same material in monkeys

Studies on Measles Joseph Stokes Jr Gerald C O Neil Morris F Shaffer Geoffrey Rake and Eliza

(4) Delaware State M J 14 193 196 September 1942

beth P Maris[5] (Univ of Pennsylvania) record (1) results following inoculation of children with egg passage measles virus and (2) results of chance and planned exposure to unmodified measles virus in children previously inoculated with egg passage measles virus

Measles virus grown on the chorio allantois of the developing chick embryo for 3 to 66 serial passages was inoculated by intranasal drip inhalation intradermal injection and subcutaneous injection into 255 children most of whom were susceptible In most of these typical reactions of extremely mild measles occurred with Koplik's *spots rash fever conjunctivitis and coryza but* rarely cough or malaise In view of the nature of the reactions, the measles virus as inoculated was considered to be modified and to produce in the children an attenuated disease Passage of the attenuated measles virus again through human beings from evidence obtained by *single human passages through several "contact control"* children showed that this virus did not regain its virulence by such human passage Reactions to the inoculations emphasized the importance of accurate negative history for measles Significant differences in the reactions to inoculation did not appear following use of different routes of inoculation two different methods for preserving the virus material and different dilutions of the inoculum

Twenty two children previously inoculated with egg passage measles virus were exposed by chance at various intervals up to one year from the time of inoculation to children with active cases of measles under field conditions Three developed typical measles 1 mild measles 3 an extremely mild disease distinguishable with difficulty as measles and 15 developed no disease

Twenty four children previously inoculated with egg passage measles virus were exposed by challenging injections of blood from patients with active cases of measles at various intervals from the time of original

(5) J Pediat 1 29 J u ry 1943

inoculation Three developed typical measles, 2 mild measles 5 an extremely mild disease distinguishable with difficulty as measles and 13 developed no disease One additional child showed slight nasopharyngitis with out fever, rash or Koplik s spots Suitable control chil dren and monkeys given portions of the challenge ma terial developed typical measles

Results of these attempts at active immunization of children against measles are sufficiently encouraging to warrant further trial in larger groups of susceptible children under field conditions since 40 of the 46 chil dren inoculated appeared to be completely or partially protected

[The two preceding articles promise that active immunization against measles may soon become practical for general use —Ed.]

MENINGITIS

Sulfadiazine Therapy of Purulent Meningitis includ ing 24 cases of meningococcic meningitis is described by Harry A Feldman Lewis K Sweet and Harry F Dowling[6] (George Washington Univ) In meningo coccic meningitis dosage schedule in adults consisted of an initial 4 6 Gm dose followed by 1 Gm every four hours Children were given approximately 0 13 Gm per kg body weight daily after initial administration of about one half the 24 hour dose Patients who were un conscious or vomiting severely were given sodium sulfa diazine at similar time intervals intravenously or subcu taneously until they were able to swallow then given oral medication Treatment was terminated abruptly after the patient had been asymptomatic for about a week

Intravenously sodium sulfadiazine was given slowly as a 1 per cent solution in distilled water Subcutaneous ly it was administered as a 0 5 per cent solution No attempt was made to adjust the dosage schedule upward unless the sulfadiazine blood level was under 5 mg per

(6) W M d 995 1007 No emb 194

100 cc If the blood level reached 15 mg or more dosage was reduced, usually by lengthening the period between administrations

Loin pain with microscopic hematuria and crystalluria developed in three patients after three to six days of therapy In view of the gravity of the disease, therapy was nevertheless continued and symptoms cleared spontaneously and rapidly No other complications of chemotherapy were noted

In 18 of the 24 patients with meningococcic meningitis temperature returned to and remained within normal limits within 48 hours after initiating sulfadiazine therapy Simultaneously there was reduction in number of leukocytes improvement in condition of the spinal fluid, rapid regression of rash when present and marked *general improvement Similar but more gradual im*provement occurred in four others who recovered. Two patients died both of whom had been admitted in a severe state of alcoholic intoxication

Four of five patients with influenza type B meningitis recovered after treatment with sulfadiazine and rabbit serum One patient died of influenzal meningitis *caused by organisms other than type B after treatment* with sulfadiazine alone

*None of six patients with pneumococcic meningitis re*covered, only two survived beyond 16 hours after admission

[Our own experienc with sulfadiazine in pneumococcic meningitis has been more *fortunate* —Ed]

Laboratory Infection with Virus of Lymphocytic Choriomeningitis Albert Milzer and Sidney O Levinson (Michael Reese Hosp Chicago) report a case in the senior author in which there is evidence that infection with the virus of lymphocytic choriomeningitis came from contact with infected monkey lice It is not known *whether* the infection came from an actual louse bite or whether it occurred as the result of skin contamination The virus was *obtained* from the spinal fluid during the

(7) J A M A 120 27 30 S pt 5 194

acute stage Specimens of serum obtained three weeks after onset at frequent intervals during convalescence and after complete recovery were titrated for both neutralizing and complement fixing antibodies against the virus Complement fixing antibodies were present three weeks after onset of symptoms and persisted at the same level for 26 months after recovery On the other hand neutralizing antibodies were not detected 3 weeks after onset but appeared after eight weeks reaching a maximal titer in 5½ months and then declining so that a constant level was reached 11 months after onset

Two Cases of Rubella Meningo Encephalitis are reported by R I C Bradford[8] one of which is presented here

Youth 19 had diagnosis of meningitis May 29 he had had a typical rubelliform rash cervical adenitis and slight malaise A rubella epidemic immediately before led to diagnosis and treatment accordingly June 1 he complained of severe frontal headache Temperature was normal the right pupil was larger than the left The next day the headache was worse temperature 100 F, pulse 80 the tongue heavily furred There was severe neck pain on flexion and Kernig's sign was weakly present on both sides Pupils were equal and reacted sluggishly to light

On admission June 2 he lay curled up in bed with his face away from the light He was somewhat drowsy but co-operative Some exposure phobia was evident The face was pale tongue furred and the remains of what might have been a rubelliform rash were present over the trunk most pronounced on the back Temperature was 100 8 F Glands in the posterior cervical triangle were enlarged and tender Koplik s spots were not present Pupils were equal and reacted briskly All reflexes were normal Babinski s and Kernig s sign were not present There was marked nuchal rigidity with pain on flexion On lumbar puncture 16 cc clear fluid withdrawn under increased pressure showed 3 cells per cu mm 160 mg protein per cent and no organisms on culture Sulfapyridine was administered as routine since several cases of meningococcic meningitis had been seen

June 3 the condition was essentially the same Kernig s sign was positive there was marked neck rigidity knee jerks were

(8) Brit M J 1 31 M 13 1943

100 cc If the blood level reached 15 mg or more dosage was reduced usually by lengthening the period between administrations

Loin pain with microscopic hematuria and crystalluria developed in three patients after three to six days of therapy In view of the gravity of the disease, therapy was nevertheless continued and symptoms cleared spontaneously and rapidly No other complications of chemotherapy were noted

In 18 of the 24 patients with meningococcic meningitis temperature returned to and remained within normal limits within 48 hours after initiating sulfadiazine therapy Simultaneously there was reduction in number of leukocytes improvement in condition of the spinal fluid rapid regression of rash when present and marked general improvement Similar but more gradual improvement occurred in four others who recovered Two patients died both of whom had been admitted in a severe state of alcoholic intoxication

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Except in localized outbreaks where contacts are known atypical (virus) pneumonia seems to be a sporadic infection arising unheralded as though either the patient had a latent infection which was activated by unfavorable physical or environmental conditions or the disease was transmitted by carriers who had only a mild headache or a simple afebrile tracheobronchitis The histories of these cases repeatedly indicated that another member of the family had an episode of headache and dry cough two to three weeks before the patient became acutely ill Fall and early winter are the most common seasons of attack of both pneumonia and the nonbacterial tracheobronchitis This is entirely analogous to the frequency of ornithosis infection in birds with onset of the cold weather when the disease is activated in carriers and new and more fulminating infections begin to appear in other birds

Acute atypical pneumonia is defined as a form of interstitial bronchopneumonia not usually accompanied by secondary bacterial invasion and characterized by bradycardia headache dry cough low or normal white count and failure to respond to sulfonamides While the term may well be used when no causal agents have been identified when they can be isolated in cases of this type they are found to belong to a related group of viruses The first isolated example of this type of pneumonia is psittacosis or ornithosis Interstitial pneumonia has also been described in cases of influenza measles pertussis and varicella and in these instances may be due entirely to action of either a virus or a bacterium or frequently to a combination of the two It has also been observed in the course of acute rheumatic fever (rheumatic pneumonia) and after irradiation of the thorax and for that reason probably represents a pathologic response to a number of types of pulmonary irritants

Comparison of the incubation period symptoms clinical course pathologic and laboratory findings in ornithosis with those in the human atypical pneumonia group

rather brisk, and plantar response was doubtful June 5, neck rigidity was less severe, there was a flexor plantar response, knee jerks were normal, Kernig's sign was absent, but fever persisted On lumbar puncture, 20 cc clear yellow fluid withdrawn under pressure contained 100 mg protein per cent and 20 cells per cu mm predominantly lymphocytes On June 6 the condition was improved, temperature was 99 F June 8 the temperature was rising but there was no clinical change June 12 a general marked rubelliform rash, pink and papular, was again present on the trunk and proximal part of the limbs, with a few spots on the face but no Koplik spots There was tender cervical adenitis, and temperature was 100 F Neurologic examination was negative Lumbar puncture disclosed clear fluid not under pressure containing 50 mg protein per cent and 50 cells per cu mm, 96 per cent lymphocytes June 14 the rash had disappeared and the only remaining symptom was a slight headache

In view of the typical rash diagnosis of rubella is most likely Occurrence of a second rash although rare is not unknown *Cerebrospinal fluid findings are interesting* in view of the marked increase of protein, especially with regard to its dissociation from the cell count Similar dissociation is found with cerebral arteriosclerosis and some cranial and spinal tumors

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PSITTACOSIS

Ornithosis (Psittacosis) During an 18 month period in which 3 cases of ornithosis were observed Cutting B Favour[9] (Harvard Univ) also observed more than 12 cases of human atypical (virus) pneumonia representing all the clinical types of the group from the rapidly fatal fulminating infection to the mild case with an unsuspected patch of consolidation found only on roentgen examination In every case it has been possible to match the clinical picture and course of these *human atypical pneumonias with that which has been* outlined for psittacosis The same parallel is evident in larger series reported by Murray, Longcope Reiman and others

(9) Am J M Sc 205 162 187 February 1943

although roentgenograms of the chest will show a central pneumonia A few chest findings may appear on the fourth day or the patient may recover without developing the signs of pneumonia Sometimes the atypical pneumonia patients show an elevation in the white count to 17 000 or more during recovery In ornithosis it does not often rise to as high a level

The more severe type of infection common in the older age groups with both atypical pneumonia and ornithosis the cause may run for one or more months In each disease there is a typhoid like state and a migrating pneumonia a high temperature with minor fluctuations and a tendency to relapse Usually children under 10 do not contract ornithosis on exposure however atypical pneumonia has been described as a severe childhood infection and is especially fatal in infants. In both diseases relative bradycardia for the first week or more later giving way to normal or fast pulse constipation and distention are consistent findings Languor severe headache and a paroxysmal dry cough persist throughout The pneumonia in both diseases is alike It is a central patchy migrating pneumonitis usually giving fewer physical than roentgen signs The density is a fine mottling an atelectasis or frank consolidation Cyanosis out of proportion to the area involved and asthmatic episodes often complicate the picture

The third type of atypical pneumonia characterized by a rapidly fatal spreading pneumonia with dense consolidation or a long course with a predilection for the age extremes or those with underlying chronic disease and also by a migrating pneumonia and high fever is similar to the severe form of ornithosis A variety of bizarre manifestations may also be present in atypical pneumonia Migrating polyarthritis erythematous skin eruptions jaundice hematuria fibrinous pericarditis general glandular enlargement encephalitis and thrombophlebitis occur In all types of both ornithosis and

reveals striking similarities Virus studies and serologic *tests also indicate close relationship in these diseases*

The incubation period for atypical pneumonia is identical with that for ornithosis—a range of 7 to 21 days usually 11 14 days Also, the infectiousness in virus pneumonia may be as great as in ornithosis

In atypical pneumonia there is usually a one to three day onset with malaise chilly sensations or occasionally a frank shaking chill Cough may initiate the illness and often there is minimal coryza with occasional epistaxis Nausea vomiting and diarrhea are uncommon Acute *symptoms are preceded by a rapid rise in temperature to* 104 F with a relative bradycardia. A hacking cough and severe headache are almost constant symptoms A typhoidal languor photophobia and conjunctival suffusion are usually present The tongue is furred, and unless there is a superimposed streptococcic pharyngitis the throat is benign Occasionally glandular enlargement, rashes or a meningitis are seen Much the same early signs are characteristic of ornithosis

The comparison is equally good between the laboratory data in the two conditions In atypical pneumonia the white count is low or normal with 70 to 90 per cent segmented neutrophils Initially there may be mild albuminuria and a low sedimentation rate During the course the sedimentation rate rises to 30 or 40 mm per hour Routine cultures of the blood throat stools sputum and throat washings usually do not yield any pathogenic organisms in abundance If the course is rapidly fatal in either ornithosis or atypical pneumonia the white count may be 20 000 or more

The cases of either disease may be classified into three general clinical types of severity There are the mild infections lasting one to seven days occurring in young adults and characterized by malaise muscle aches headache and a variable amount of nonproductive cough Physical examination is negative the first three days

was either a negative reaction or at most positive fixation in dilutions of 1 2 during the late acute phase of the illness None showed a rise in titer or positive fixation during convalescence Other serologic procedures are needed in studying this type of infection to detect the presence of latent infections as well as outspoken cases of human atypical pneumonia Only then will it be possible to show how endemic in man is atypical pneumonia and what can be done to control it

It is suggested that cases of human atypical pneumonia from which no etiologic agents have been isolated may be due to a virus of the psittacosis group which has become fixed in man and is usually incapable of heterogeneous parasitism

[This article might also be entitled Atypical Pneumonia It throws important light on a disease of undetermined etiology — Ed]

Psittacosis (Ornithosis) Virus in English Pigeons C H Andrewes and K C Mills[1] (Nat l Inst for Med Research) recovered psittacosis virus from apparently normal pigeons obtained from two sources in southern England and pigeons recently arrived from America Experiments with pigeons from another English source gave inconclusive results

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POLIOMYELITIS

Pathology and Pathogenesis of Human Poliomyelitis Albert B Sabin[2] (Univ of Cincinnati) states that study of the distribution of virus in various parts of the body of persons dying of poliomyelitis has thrown considerable light on the tissues predominantly attacked in human poliomyelitis Results of tests on 22 different tissues from each of seven cases indicated that the virus is found predominantly in two systems in certain regions of the nervous system and in the alimentary tract Its absence from the olfactory bulbs and associated rhinencephalic

(1) L n et 1 29 94 M 6 1943
(2) J A M A 120 506 511 Oct 17 194

atypical pneumonia the roentgen changes may persist from a few days to weeks after the patient becomes afebrile

Pathologically the findings in atypical pneumonia are similar to those of ornithosis and other known virus pneumonias *It is as if the body tended to respond in a similar manner to a variety of closely related but distinct pathogenic agents* Grossly, the lungs in atypical pneumonia may show loose adhesions connecting the lobes and a fibrinous exudate over the visceral pleura A patchy consolidation resembling confluent lobular pneumonia areas of atelectasis or what appears to be pulmonary edema may be present The small bronchi contain a thick mucopurulent exudate consisting chiefly of polymorphonuclear leukocytes and show congestion of their mucosa The early lesions are a hemorrhagic *alveolitis and an interstitial bronchitis and tracheitis* with squamous metaplasia and segmented neutrophilic infiltration in the bronchi and a mononuclear response in the alveoli These are almost identical with the findings in ornithosis In the later stage of atypical pneumonia, the septums become thickened by rows of mononuclear cells about the alveolar periphery which infiltrate the septal walls, as well as by a tendency to organization with fibroblastic and endothelial cell proliferation The most interesting findings of atypical pneumonia are vascular and perivascular lesions in the lung *capillaries and in the medium sized branches of the* pulmonary arteries showing a neutrophilic mononuclear and eosinophilic infiltration reminiscent of periarteritis nodosa

Two of Favour's three patients with ornithosis had a high titer of psittacosis antibody in their immediate convalescent serum The third had a convalescent titer which was moderate and well may represent a cross reaction so common in this general group of infections The same complement fixation test for psittacosis was done in most of the other atypical pneumonia cases and in all there

to the extent that in some instances no lesions may be present in the highly susceptible lumbar cord

The reverse obtains in the primary spinal type Here the lesions are concentrated in the entire spinal cord and although present are less pronounced in the medulla Since in man the virus is predominantly situated in the alimentary tract the neural connections between it and the central nervous system are reviewed There is every possibility and suggestive evidence that the virus may invade along the fifth seventh ninth and tenth cranial nerves from the upper part of the alimentary tract to cause primary bulbar poliomyelitis Absence of virus from the superior cervical sympathetic ganglions in six human cases and in the orally infected cynomolgi suggests that this sympathetic pathway leading to the upper thoracic cord is probably not utilized When the primary paralysis affects the lower extremities intercostals and also upper extremities the visceral afferent fibers from the intestine via the dorsal root ganglions probably provide the usual pathway for invasion of the central nervous system Tests on the celiac plexus in eight human cases yielded virus in only one and even in that one the primary paralysis was bulbar no virus was obtained from the celiac plexus of any of five orally infected cynomolgi These findings tend to militate against the visceral efferent pathway via the collateral sympathetic ganglions such as the celiac as a common route for progression of virus from the intestine to the spinal cord Finally there is every possibility that the vagal afferent and efferent pathways between intestine and medulla may be utilized by the virus

Epidemiologic and Experimental Observations on Possible Significance of Rodents in a Suburban Epidemic of Poliomyelitis Claus W Jungeblut (Columbia Univ) and Gilbert Dalldorf[3] (Valhalla N Y) isolated a rodent pathogenic virus which paralyzes albino mice

(3) Am J Pub H lth 33 169 17 F bru ry 1943

centers and from the nasal mucosa indicated that the olfactory pathway is not the usual port of entry The almost regular presence of the virus in the walls of the pharynx or ileum or in the intestinal contents and its absence from most of the other tissues tested suggested that the alimentary tract may be the first site attacked Tests on various levels of the human alimentary tract revealed the virus in washed portions of the tongue posterior pharyngeal wall duodenum and various levels of the small and large intestines In experimental poliomyelitis produced in cynomolgus monkeys the virus was found not only in the walls of almost the entire alimentary tract but also in liver, spleen kidneys urinary bladder and certain lymph nodes as well as in the blood at the time of paralysis Despite this widespread dissemination the virus was not present in the cerebrospinal fluid and its distribution in the nervous system was similar to that found in human beings Distribution of lesions and virus in the nervous system of man and experimental animals does not correspond to that expected from indiscriminate spread across the blood vessels or dissemination via the cerebrospinal fluid with *ultimate localization dependent on the special susceptibility of certain cell groups*

Doubtless some neurons are more susceptible than others to the effects of poliomyelitis virus but evidence *indicates that the part of the central nervous system first* attacked by the virus is determined by the neural connections of the peripheral tissue from which the virus invades and that subsequent spread in the nervous system *depends on the central connections of the neurons in* which the greatest proliferation of the virus occurs In the typical primary bulbar case of short duration there is particularly heavy concentration of neuronal lesions in the medulla especially near the nucleus ambiguus dorsal motor nuclei of the vagus and nucleus solitarius with a smaller number as the spinal cord is descended

rather simultaneous infection from some uncovered common source at the time when the two individuals were in contact with each other Thus in these exceptional instances where time of exposure to a previous case can be determined an infectious period extending from four days before to five days after onset of symptoms is indicated

The minimal maximal and actual intervals between exposure and onset for the 49 cases was determined. In 18 the maximal interval ranged from 6 to 14 days and in 17 of these this was the actual interval (following a single exposure) The minimal interval ranged from 1 to 20 days, but in the 14 cases showing a minimal interval under six days exposure was such that the incubation period could have been longer Thus the incubation period indicated by these intervals appears to range from 6 to 14 days and exceptionally to extend to 20 days

Immunity to Poliomyelitis W Lloyd Aycock[5] points out that discrepant neutralization tests in poliomyelitis (which have in the past been interpreted as indicating that on the one hand immunity as shown by the neutralization test is not indicative of protection against infection with the virus and on the other hand it does not follow infection with the virus) appear to be due to use of heterologous strains of virus

When human convalescent serums from cases occurring in an outbreak in which the epidemiologic evidence indicated infection with a single strain of virus were tested against that strain neutralizing antibody was regularly found while in tests against an old laboratory strain only a portion had neutralizing antibody Monkeys convalescent from an attack from each of two strains of virus neutralized the homologous virus but not the heterologous strain Monkeys convalescent from separate attacks from the two strains of virus neutralized both strains Normal adult serums from many parts

(5) Am J M S 204 455 467 S ptembe 1942

cotton rats and hamsters from the brain of a house mouse found dead in the home of a patient who died of poliomyelitis Another rodent pathogenic virus capable of inducing paralysis in albino mice cotton rats and hamsters was isolated from the brain stem of the patient The two viruses when passaged in albino mice are similar in that both are completely inactivated by antiserums against Theiler's virus of mouse encephalomyelitis and show some neutralization with convalescent serums from patients involved in the epidemic However they differ markedly in virulence for albino mice in that the human virus is much more potent than the mouse virus

Infectious Period of Poliomyelitis and Virus Detection W *Lloyd Aycock* and *John F Kessel*[4] present data on 49 cases which followed a limited exposure to a previous case These afford an indication either of the earliest latest or actual date with reference to onset of the primary case when infection of the secondary case could have occurred In 18 cases the first exposure (but not necessarily the last) fell in all but 2 between the fourth day before and the fifty day after onset of the primary case in all but 1 of the 49 cases the last exposure *(not necessarily the first) was not later than the* fifth day of the disease in the primary in 17 cases there had been but a single exposure this falling in 16 between the fourth day preceding and the fifth day following onset of the primary In five of the six pairs of cases in which the last exposure to each other occurred earlier than the fifth day before the beginning of symptoms in the first case the onsets in the two cases were practically simultaneous and occurred in both at an interval following the exposure to each other corresponding to the incubation period of the disease These instances suggest that as a group the cases in which exposure took place upward of two weeks before onset of the first case represent not secondary infection one from the other but

(4) Am J M S 205 4 4 465 March 1943

[These contributions to our knowledge of poliomyelitis show that constant advances are being made and that the conquest of the disease is well under way —Ed]

RHEUMATIC FEVER

Clinicopathologic Study of Rheumatic Fever and Rheumatic Heart Disease in White and Negro Races Francis L Bruno and Hugo T Engelhardt[7] (Charity Hosp New Orleans) studied the discharge diagnoses of 187 987 case histories from 1939 to 1941 and found 150 cases of acute rheumatic fever an incidence of 0 08 per cent Forty four per cent were in Negroes and 56 per cent in white patients In this interval were 725 instances of rheumatic heart disease 51 per cent of which occurred in white patients and 49 per cent in Negroes There was no appreciable difference in active and inactive rheumatic heart disease

Data from 16 121 autopsies disclosed 102 cases of rheumatic heart disease 46 in whites and 56 in Negroes These statistics suggest that Negro patients with rheumatic heart disease tend to die at an earlier age than do white patients

Wartime Decline of Acute Rheumatism A study of mortality statistics has led J Alison Glover[8] to conclude that in England there has been a noticeable reduction in cases of rheumatic fever chorea and rheumatic heart disease since 1939 Rheumatism schemes supervisory centers and provisions of hospital and convalescent home accommodations for rheumatic children important preventive measures as they are can hardly have been developed enough before about 1930 to influence the decline appreciably Their efficiency was not increased by war and can hardly be related to the sudden acceleration of the decline since the war began

The decrease in poverty caused by abundant employment during wartime the greatly increased provision of

(7) N w O l M & S J 95 34 38 No mb 194

(8) L n et 2 51 52 J ly 10 1943

of the world have been studied and found to neutralize a number of strains of virus with equally high frequency

It is suggested that the momentary immunity status of individuals is represented by the presence of neutralizing antibody to strains to which the individual has been exposed previously, and the end point of immunity (adult) by the presence of neutralizing antibody to a number of strains

It appears therefore, that the several strains of virus are all in equally free circulation and attain an equally widespread dissemination Furthermore, there are indications that a given outbreak may not be caused primarily by the introduction of a single strain (from a single case) but may be precipitated by other factors on a background of subclinical carriage of a number of strains

Ultracentrifuge as Aid in Detection of Poliomyelitis Virus Joseph L Melnick[6] (Yale Univ) reports that by differential ultracentrifugation a purified and concentrated macromolecular fraction has been regularly obtained from infected human monkey and chimpanzee stools Poliomyelitis developed in 15 of 16 monkeys inoculated intracerebrally with the fraction isolated from 16 stools in which virus was thought to be present Eleven stool specimens in which virus was suspected when tested separately in 11 monkeys by the intra abdominal intranasal method produced poliomyelitis in 2 The same specimens tested separately by the ultracentrifugal intracerebral method produced poliomyelitis in 10 of 11 monkeys inoculated With the intra abdominal–intranasal method it has been customary to inoculate the virus present in 1 6 Gm stool With the ultracentrifugal intracerebral method the virus present in as much as 30 Gm stool has been inoculated From one titration experiment it appears that the ultracentrifugal intracerebral method is 100 times more sensitive than the intra abdominal–intranasal method

(6) J E p r Med 77 195 04 M 1 1943

and incapacitating disease most of these patients should be recommended for invaliding from the army

Toxic arthritis which tends to occur in the older soldier, may closely simulate rheumatoid arthritis but is associated with a definite focus of infection Swelling pain and tenderness not necessarily symmetrical may occur in any joint Constitutional disturbance is seldom marked and pyrexia is uncommon, unless sepsis is severe Sedimentation rate may be increased or normal Leukocytosis may occur Osteoporosis and muscular wasting if present are confined to the affected joint region Treatment includes removal of septic foci and rest and counterirritation of affected joints Some patients may require regrading in the service because of the likelihood of recrudescence others may be gradually rehabilitated.

Gonorrheal arthritis is difficult to diagnose and is probably less uncommon than is generally supposed Diagnosis is based principally on a history of gonorrhea After a polyarticular migratory phase the condition is often localized to one joint the commonest sites being the knee carpus tarsus and sternoclavicular joints The joint is red tender and swollen General constitutional disturbance is uncommon pyrexia may be present tenosynovitis is frequently present and there is no marked osteoporosis Gout should be remembered in differential diagnosis Hyperpyrexia is the therapy of choice Although treatment may be fairly prolonged most patients should eventually be fit for return to their unit or for regrading in a lower category

Fibrositis is the commonest chronic rheumatic disease in the army Objective indications are difficult to evaluate and patients are often classed as malingerers Complaints are pain stiffness and tenderness in certain places If the patient is placed so that the muscle involved is fully relaxed and the tender spots can be palpated against subjacent bone hard fibrous nodules and bands can often be felt Constancy of location of a

milk for all children and of solid meals for school children and the long "changes of air" due to evacuation which have tended to decrease urbanization are all possible factors in the suddenly accelerating decline But beyond and above these factors, the facts suggest that the main cause for the decline is a change in the relationship between man and Streptococcus pyogenes This may be constituted by an increasing immunity of man to Streptococcus pyogenes or by a decreasing ability of the organism to provoke the rheumatic reaction, just as it seems to have become less toxigenic as measured by the incidence of scarlet fever

Diagnosis and Treatment of Chronic Rheumatic Diseases in Soldiers R G Gordon and G D Kersley[9] state that the principles presented are somewhat dogmatic and consequently will apply to most, but not all, cases Moreover suggestions on length and type of treatment and disposal of cases apply to the services at war, and some may not be applicable in peacetime in civil or military life

Rheumatoid arthritis occasionally occurs in young soldiers Points in early diagnosis include symmetrical swelling pain and tenderness especially of small joints wrist and knee considerable constitutional disturbance sometimes with mild pyrexia increased sedimentation rate osteoporosis and muscular wasting in general. Blood changes such as anemia and an Arneth shift to the left may be present Treatment requires hospitalization Rest feeding and fresh air are prime requisites Specific treatment including the use of gold and removal of foci of infection should be undertaken only after consultation General progress is best indicated by the sedimentation rate Only conservative hydrotherapy or physical therapy is indicated in the early stages Correct orthopedic position of joints must be maintained if necessary by plaster As this is a prolonged progressive

(9) J R y Army M C rps 79 133 139 Septembe 194

will improve sufficiently to be capable of a high degree of efficiency, though in a lower medical category

Rheumatic Fever in the Navy Arthur M Masters (M.C U S N R) discusses the significance of 80 cases of rheumatic fever among naval personnel. These cases were of the classic variety the average age of the patients was 21 Most frequently the attacks occurred in the winter and spring following an upper respiratory tract infection associated with physical exertion fatigue and often mental strain The boys came from the west coast training camps from the South Pacific from ships on which they had stood watch from ships that were sunk and from the Solomons Some had suffered from prolonged immersion others had experienced severe ordeals on Guadalcanal With the unaccustomed physical strain there had been concentrations of a large number of men The attacks often took place within a few weeks after enlistment

It is significant that nine of these cases developed in the South Pacific a tropical region Of most importance however is the fact that in 54 per cent of the cases a past history of one or more attacks of childhood rheumatic fever has been obtained This incidence is probably even higher Masters concludes that the recruit who gives a previous history of rheumatic fever should not be accepted in the armed forces and once he develops rheumatic fever while in the service he should not be retained

( ) U S N v M B ll 41 1019 10 1 J ly 1943

tender spot on successive examinations indicates genuine disability. Pain is not always localized at the tender nodule. It can often be elicited by stretching the muscle either by active or by passive movement so as to pull on the nodule. Constancy of this finding also signifies genuine disability. Subcutaneous tissue, intramuscular trabeculae, fascia, tendon junctions to muscle or bone, and periarticular and perineural tissues may all be involved in the fibrositic process. There is no appreciable general disturbance except after prolonged pain; no pyrexia and no change in blood count or sedimentation rate. Roentgenograms reveal no bony changes.

The acute pain of fibrositis may be dramatically relieved by injection of a local anesthetic into the tender spot. Failure of such therapy militates against the diagnosis of fibrositis, and if no other cause of pain is discovered the nature of the patient's subjective complaint should be suspect. This treatment is sometimes adequate, but more commonly aching and stiffness persist. In such cases massage and heat or spa treatment is indicated.

Management of Rheumatic Disease in the Forces. According to Oswald Savage[1] soldiers with rheumatic disease should be hospitalized so that they may be rendered fit for full duty in as short a period as possible. A soldier with rheumatic disease is of no use in his unit and will usually be stationed too far from a physical therapy department to be able to go for daily treatment. Therefore, in many cases the most rapid way to return a man to his full duties is to admit him to the hospital where *intensive treatment can be given.* Often after a short period in the hospital he can be transferred to a convalescent depot where treatment can be continued under physical training instructors with the supervision of the command specialist in physical medicine.

Owing to the type of rheumatic disease encountered in the services a large proportion of patients can be completely cured, while those with the more chronic cases

(1) B. M. J. 2:336-338, Sept. 13, 194

maximum effects when used in the first few days Chemo and serotherapy are only adjuncts to surgery and should not replace it for localized infections

Staphylococcic Infection Simulating Scarlet Fever Henry Aranow Jr and W Barry Wood Jr[4] (Johns Hopkins Univ) describe a clinical syndrome indistinguishable from that of scarlet fever and associated with staphylococcic osteomyelitis and bacteremia observed in a patient from whom no beta hemolytic streptococci could be cultured The strain of hemolytic Staphylococcus aureus isolated from the patient s blood was found to produce a filtrable erythrogenic toxin which was neutralized by commercial scarlatinal antitoxin The authors conclude that scarlet fever may occasionally be caused by an erythrogenic toxin produced by certain strains of staphylococci

[It should be kept in mind that commercial scarlet fever antitoxin sometimes contains antitoxins other than that which is specific for scarlet fever streptococcus This comes about in various ways one of which is the occurrence of infections such as staphylococcic infections in the horses used in the production of the commercial antitoxin. These other antitoxins do not in the least impair the therapeutic value of the antitoxin but do make it unsuitable for the tests for which it was used in the experiments described here —Ed]

Classification of 110 Strains of Staphylococcus Aureus Olive Durfee[5] (Pearl River N Y) studied the *agglutinative and polysaccharide forming qualities* of a collection of Staphylococcus aureus strains Most of the strains belonged to the Cowan groups I and III and produced Julianelle A polysaccharide Leukocidin positive strains belonged mainly to group II Most leukocidin positive strains showed a tendency to produce less A polysaccharide than other strains A supplementary agglutinative group is described in addition to the three Cowan groups

Slide Test for Coagulase Positive Staphylococci The clumping of thick suspensions of coagulase positive staphylococci by human citrated plasma may be made

(4) J A. M A 119 1491 1495 Aug 9 1942
(5) J Bact 44 589 595 N vember 1942

STAPHYLOCOCCUS INFECTION

Consideration of Therapy in Staphylococcus Infections R H Rigdon (Univ of Tennessee) and Paul F Stookey[3] (Kansas City Mo) state that rational therapeusis in staphylococcic infections is difficult to propound because of variation in action of different strains of staphylococci and inability to classify pathogenic and nonpathogenic strains The coagulase test may be the best method for determining pathogenicity, however division into hemolytic and nonhemolytic strains is important, and rapidity with which this division can be made is valuable clinically Hemolysis occurs earlier and forms a larger zone on blood agar mediums in which rabbit red cells are used than on any other type of blood agar medium

Staphylococci may affect the host through action of their toxins on parenchymatous tissues Exotoxin produced by staphylococci may be neutralized by specific antitoxin which must be given before the toxin becomes fixed to the tissues Toxin apparently present in over 90 per cent of cases of staphylococcic septicemia is capable of producing death or may be of only secondary importance

Action of chemotherapeutic agents apparently depends on their inhibitory influence on bacterial growth They do not neutralize staphylococcus toxin Sulfanilamide sulfapyridine and sulfathiazole have little if any therapeutic value Newer chemotherapeutic agents have not been evaluated

A combination of staphylococcus antitoxin and either sulfapyridine or sulfathiazole appears to be the best form of therapy, especially for severe staphylococcic infections with toxemia This combination is important if the staphylococcus is hemolytic and will obtain

(3) Surgery 1 635 650 October 194

STREPTOCOCCUS INFECTION

Epidemiology of Streptococcus Haemolyticus Infections at Naval Training Stations Alvin F Coburn[7] (M C, U S N R) reviews the close association between hemolytic streptococcus infection of the upper respiratory tract and activation of the rheumatic process This relationship is especially striking among the armed forces where rheumatic fever is prone to occur in explosive outbreaks following seasonal epidemics of streptococcic infection and where at other times of the year this disease appears only sporadically

Five environmental conditions favoring the development of an epidemic of streptococcic infection are frequently satisfied at a training station in time of war An understanding of these conditions may serve in helping prevent the epidemic spread of this microorganism and subsequent outbreaks of rheumatic fever These conditions are (1) susceptibility of the host to infection by Streptococcus haemolyticus (2) high rate of change of population (3) overcrowding (4) widespread activity of a respiratory virus such as that giving rise to the common cold influenza or measles and (5) the presence of one or more strains of hemolytic streptococcus endowed with great communicability

That these five conditions obtain in a training station under war conditions was recognized during World War I At that time it was observed that in a measles ward the streptococcus carrier rate rose rapidly Beginning with a carrier rate of 11 4 per cent there was a rise to 38 4 per cent in 5 days and 56 8 per cent in 16 days Excluding pneumonias measles and diseases of probable streptococcic origin there were approximately 242 000 infections due to hemolytic streptococcus This

(7) U S N M B 41 1012 1018 July 1943

the basis of slide tests for a rapid presumptive identification of potentially pathogenic Staphylococcus pyogenes (aureus) Bessie Cadness Graves, Robert Williams, G J Harper and A A Miles[6] describe a slide test whereby at least 9 of every 10 strains of Staphylococcus pyogenes that prove to be coagulase positive by the orthodox tube test may be detected The number of coagulase positive strains missed by the slide test is small in the hands of experienced workers but all slide negative strains must be tested by the tube method Coagulase negative strains do not give positive slide reactions The following routine is suggested for examination of plate cultures of Staphylococcus pyogenes

TECHNIC —Place a clean slide and a clean, grease-free slide side by side and put a drop of water on each with a 2 mm loop Rub the suspected colony into the first drop with a minimum of spreading and when the suspension is homogeneous, transfer the wet loop to the other drop (on the grease-free slide) and spread it into a thin film for staining The amount of growth picked off should be large enough or the volume of the water should be small enough to produce in the first drop a watery suspension equivalent in opacity to at least 100 × 10⁹ Bacterium coli per cc Mix a 1 mm loopful of fresh human plasma into the first drop keeping up a circular motion, 3 5 per second for 10 seconds If clumping occurs then a presumptive diagnosis of Staphylococcus pyogenes may be made confirmed by the appearance of the stained smear If no clumping occurs and the stained smear shows gram positive cocci, a broth is inoculated for a tube coagulase test by one of the accepted technics Though late clumping is suggestive it must on no account be u ed as basis of identification

(6) Lanc t 1 736 738 Jun 12 1943

and renal lesions are uncommon Suppuration in the heart muscle and in organs peripheral to the heart probably occurs uniquely in enterococcic endocarditis Administration of a sulfonamide does not sterilize the blood or affect the final outcome in these cases but may cause the temperature to return to normal for a brief period

Enterococci usually in association with coliform bacilli, are a common cause of peritonitis and other infections in and about the abdominal cavity This is especially true if perforation of the gastro intestinal tract has occurred Presence of fecal streptococci in the heart's blood post mortem in several cases of peritonitis indicates that sepsis due to these organisms may often occur Their relationship to fatal outcome in cases of acute infections of the abdomen should be further studied.

Culture of the urine frequently reveals enterococci in large numbers In many instances no evidence of infection can be discovered. When it is other organisms are usually associated with the streptococci Treatment with a sulfonamide results in elimination of bacteria other than the enterococci and disappearance of all signs of active disease These observations demonstrate the slight inflammatory properties of the enterococci in relation to the urinary passages Occasionally this group of organisms does cause cystitis or pyelonephritis and these infections are remarkable principally because of their failure to respond to sulfonamides

Results of this study indicate that the enterococci are of relatively low virulence and invasiveness but that they are not infrequently responsible for serious local or generalized infections Hemolytic enterococci may be readily confused with the important members of group A if methods of identification are not precise The nature of the infectious process and the response to therapy

was an incidence of 7 per cent of the mean annual strength of the armed forces, among which were recorded 56 000 cases of rheumatic fever or rheumatism. *Outbreaks* of rheumatic fever *following* epidemics of streptococcic infection have already been observed in World War II in training centers in England and America It is clear that the problem of such epidemics with the subsequent development of rheumatic fever is of great importance

Enterococcic Infections Lowell A Rantz and William M M Kirby[8] (Stanford Univ) evaluate the importance of fecal streptococci and related organisms in the causation of human disease The enterococci form a group of hemolytic and nonhemolytic streptococci of special biologic and serologic properties whose normal habitat is the human bowel They are exceedingly resistant to the bacteriostatic action of the sulfonamides

Recent observations have shown that these organisms are *more frequently* isolated *from* human clinical sources other than the respiratory tract, than any variety of streptococci Fecal streptococci are infrequently responsible for disease of the respiratory tract, but seven cases of otitis media have been observed in which they were etiologically involved The disease is different from the usual streptococcic infections of the ear in that it occurs in infants and appears to have a shorter and milder course A peculiar localized subacute meningitis associated with sepsis developed in one adult

Enterococci are responsible for approximately 20 per cent of all cases of subacute streptococcic endocarditis The clinical course of the infection in these cases resembles that caused by the more frequently isolated types of streptococci but certain differences are apparent The normal heart is more likely to be affected,

(8) *Arch Int M d 71 516 5 8 April 1943*

TETANUS

Tetanus Toxoid Immunization of Adolescents J Roswell Gallagher Constance D Gallagher and Gustav G Kaufmann[3] (Phillips Academy Andover Mass) administered two immunizing doses of tetanus toxoid to 509 boys aged 13 19 years without subsequent development of serious local or systemic reactions The incidence of unfavorable reactions however was apparently higher in this group than among either younger or older subjects Strongly positive skin reactions to diluted tetanus toxoid were recorded in 3 7 per cent of the group 1 boy developed urticaria 2 boys developed sterile abscesses and 12 had sufficient malaise and fever to warrant infirmary care for 24 hours

There is apparently little relation between known previous allergic states and skin sensitivity to diluted tetanus toxoid Neither skin sensitivity to diluted tetanus toxoid nor elicited previous history of allergic manifestations was found to be a reliable criterion on which to predict skin sensitivity or the development of unfavorable local or systemic reactions Fifteen of the 19 boys whose skin tests were strongly positive were given toxoid in four divided doses no unfavorable reactions occurred in this group

Until further experience with this age group is evaluated it is suggested that skin tests with diluted tetanus toxoid be made prior to administration of each immunizing dose

Active Immunization of Human Beings with Combined Clostridium Perfringens and Tetanus Toxoids Sarah E Stewart[4] (U S Pub Health Service) reports that use of concentrated Clostridium perfringens toxoid suspended in plain tetanus toxoid induces combined immunization both in guinea pigs and in human beings

(3) N w E gla d J M d 227 691 694 No 5 194

(4) W Med 3 508 511 M y 1943

of disease caused by the two groups of organisms are not the same the importance of accurate differentiation between them is therefore obvious

Anaerobic Nonhemolytic Streptococci in Surgical Infections on a General Surgical Service William Roberts Sandusky, Edwin J Pulaski, Balbina A Johnson and Frank L Meleney[9] (Columbia Univ) review the literature on this group of organisms Save for their role in puerperal infections their significance is generally *not appreciated* The *organisms form a part of* the normal flora of the human mouth intestine and female genital tract They are usually present in the role of harmless saprophytes however, under certain conditions because of alterations either in the bacteria themselves or in the host or because of symbiosis with other micro organisms they are capable of producing inflammatory processes in various body tissues and organs

Among the infections in which these organisms play a part are certain infections of surgical significance The authors report 170 cases of various types of surgical lesions occurring on a general surgical service from which the organisms were isolated Twenty nine of the cases showed anaerobic nonhemolytic streptococci in pure culture Recovery of these organisms in pure culture as well as in association with other organisms from perirectal abscesses infected pilonidal cysts and infected sebaceous cysts is reported for the first time Adequate bacteriologic study of all surgical infections should therefore include a search for these organisms and other anaerobes as well as those of aerobic variety

There is as yet no adequate system for classification of the anaerobic nonhemolytic streptococci

(9) S g Gynec & Ob t 75 145 156 A gust, 194

occasionally chills and fever, resembling those following typhoid vaccination but occurring less frequently Those in the second category usually occur within 30 minutes after injection They are characterized in general by flushing and itching of the skin local and generalized urticarial eruptions and edema of lips and eyelids Occasionally there are edema of the glottis and dyspnea Such reactions occurred in only about 1 of every 2 000 injections following discovery that toxoids containing Witte or Berna peptones were responsible the incidence has fallen to less than 1 in 10 000 injections Toxoids in current use contain certain peptones and other proteins which may be potential sensitizing agents giving rise to occasional primary reactions and shown to be capable of producing positive skin tests in individuals who have previously reacted to Witte and Berna peptone toxoids

Tetanus in the Immunized Subject H Bathurst Norman[6] reports a case of tetanus in a soldier who had earlier received two injections of protective toxoid This case emphasizes the wisdom of the recommended procedure of giving renewal doses at 12 month intervals

Soldier 27, was hospitalized Nov 13, 1942 with the complaint of increasing pain and stiffness in the back for four days There had been septic sores on both legs for 14 days before admission He had been inoculated with 1 cc tetanus toxoid prophylactically on Nov 18, 1940 and again on Jan 13 1941 Pain began in the lumbar region at first in spasmodic attacks The attacks gradually increased in frequency and intensity until spasm was tonic and the pain severe and continuous The back became arched and could not be straightened Occasionally more intense spasms were superimposed on the tonic contraction No stiffness of the jaw or facial muscles had been noted

On admission there was considerable opisthotonus with spasm of the erector spinae muscles more definite on the left than on the right The abdominal muscles were rigid All tendon reflexes were increased and a positive jaw jerk was elicited There was some fibrillary twitching of the thigh muscles Occasional reflex spasms were observed during the

(6) La t 1 557 558 M y 1 1943

as evidenced by antitoxin titrations The antitoxin response to tetanus toxoid is greater when the toxoid is given in combination with Clostridium perfringens toxoid than when it is given alone According to previous work, guinea pigs so immunized show ability to withstand large doses of a living culture of Clostridium perfringens inoculated intramuscularly On the basis of analogy there is reason to believe that the same might be the case in human beings in whom chance infection probably does not involve many spores

Tetanus Toxoid Its Use in the United States Army Arthur P Long[5] (M C, U S A) states that use of toxoid for development of adequate protection against tetanus involves establishment of a basic active immunity and subsequent re enforcement by administration of stimulating or booster, doses

All military personnel are given three subcutaneous injections of 1 cc tetanus toxoid at weekly intervals *Ordinarily a single stimulating dose of 1 cc toxoid* is administered a year after the initial series As added safeguard a single stimulating dose of 1 cc is administered during the month prior to departure for a theatre of operations unless this is within six months of administration of a previous dose

An emergency stimulating dose of toxoid is administered on incurrence of wounds or severe burns in battle at the time of secondary operations or manipulations of old wounds or at any other time when danger from tetanus is feared Antitoxin is not administered for prophylaxis unless it is doubted that the individual had previously received at least the initial series of toxoid *injections* If such doubt exists a prophylactic dose of tetanus antitoxin is administered and active immunization with toxoid is simultaneously initiated

Reactions to tetanus toxoid are classified in two main *categories* Those in the first category cause no concern headache weakness general malaise local soreness and

(5) Am J Pub Health 33 53 57 January 1943

irregular relapsing fever, lymphadenopathy splenomegaly eosinophilia nephritis neuritis, and periarteritis, polyarteritis and panarteritis Yet prolonged fever pseudoparalysis, splenomegaly, asthma, albuminuria and cylindruria may occur in the course of trichinosis Asthma however, antedated the disease described by many months The pain in the legs, tingling numbness and footdrop seemed more likely to be the result of neuritis not myositis The periorbital edema may have been related to nephritis

Study of the patient nearly two years after onset of illness revealed no clinical, microscopic or serologic evidence of either disease but only a progression of the nephritis and cardiac failure which are common terminal events of periarteritis nodosa

Several possibilities are suggested to account for the patient s illness (1) periarteritis nodosa of which the acute stage had passed leaving lesions which healed or disappeared with the exception of the renal ones which are progressive (2) repeated infections with trichinella or chronic trichinosis with unusual manifestations since the precipitin test is supposedly reliable as a confirmatory test and negative cutaneous tests usually thought to be more reliable do not necessarily exclude the diagnosis (3) both trichinosis and periarteritis nodosa in the same patient either one preceding the other or (4) an underlying allergic condition which may be regarded as definite, since many members of the patient s family had allergic diseases and the patient had asthma It is possible that trichinosis which is also characterized by allergic manifestations may have aggravated the existing condition or even caused it and brought about the *microscopic reaction and subsequent disease regarded as* periarteritis nodosa

A similar diagnostic problem existed in the second case At necropsy however no evidence of periarteritis nodosa remained but trichinellae were found in the muscles These cases suggest the possibility that trichinosis as a disease with strong allergic manifestations may in certain instances serve as one cause of the syndrome called periarteritis nodosa

first three days of the illness Neither trismus nor dysphagia was noted Temperature and pulse were elevated during the three days after admission the temperature reaching 100 F on the second day There were a number of septic skin lesions on both legs some of which yielded a sanious discharge while others had healed with scab formation

The patient was given 200 000 units of antitetanic serum intravenously immediately after admission The reflex spasms were readily controlled by administration of 15 gr each of chloral hydrate and potassium bromide, four times daily The septic areas on the legs were treated with hypertonic saline dressings and later with 1 per cent gentian violet applications No further antitetanic serum was given Apart from the appearance of an urticarial rash which persisted for two days recovery was uneventful

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TRICHINOSIS

Trichinosis and Periarteritis Nodosa Hobart A Reimann Alison H Price and Peter A Herbut[1] (Jefferson Med College) review two cases illustrating problems *in diagnosis which may arise in trichinosis or periarteritis nodosa* and evidence of a possible relationship of the two diseases

Trichinosis was strongly suspected because the patient had eaten poorly cooked pork for months The illness apparently began acutely with bloody diarrhea and fever, followed by pain in the calf muscles, periorbital edema leukocytosis and eosinophilia, microscopic evidence was suggestive, and precipitin tests with trichinella antigen were positive in high dilution Only the absence of trichinellae in the muscles and negative cutaneous tests and complement fixation reaction weakened the diagnosis Such discrepancies, however are common in trichinosis Restudy of muscle tissue strongly suggested periarteritis nodosa Nevertheless, trichinosis being the more common disease, was still favored since even though trichinellae were not seen in the muscle inflammatory changes such as were present may occur in adjoining muscle fibers and connective tissue

As the disease progressed over many months the points in *favor* of a diagnosis of periarteritis nodosa seemed to gain weight, particularly the history of asthma starting two years before the present acute episode and persisting the prolonged

(1) J A M A. 1 ? 274-279 M y 9 1943

TULAREMIA

Vaccine Prophylaxis against Tularemia in Man is evaluated by L Foshay W H Hesselbrock H J Wittenberg and A H Rodenberg[7] (Univ of Cincinnati) From 1933 to 1941 they vaccinated 2 145 susceptible individuals exposed to infection using a vaccine made by oxidation of virulent strains of Pasteurella tularensis with nitrous acid The turbidity and duration of oxidation of the vaccine used were not constant throughout the series but since 1936 a T 6 000 four hour oxidized vaccine has been used The mode of administration however was uniform Three 0 5 cc doses were injected subcutaneously and alternately into the arms on either consecutive or alternate days It was found advisable to complete administration within six days for a delayed third injection frequently provoked constitutional reactions and unduly large local reactions After adoption of the T 6 000 four hour oxidized vaccine constitutional reactions were provoked by the initial dose of 0 5 cc in about 60 per cent of individuals on annual revaccination Thereafter all applicants were given a trial first injection of 0 25 cc The second and third doses varied in accordance with appearance and degree of reactions If both general and local reactions were marked no more vaccine was given that year If there was no general reaction but marked local reaction the subsequent doses were 0 25 cc each If neither general nor undue local reaction occurred the subsequent doses were 0 5 cc each This plan gives maximal protection at minimal physiologic cost

It is unnecessary and inadvisable to vaccinate persons who have recovered from tularemia. Since they are already protected for life the general and local reactions of unusual severity which inevitably follow serve no

(7) Am. J Pub H lth 32 1131 1145 October 1942

Incubation Period of Trichinosis was found to be 22 days or less in 98 per cent of 156 cases studied by O R McCoy[2] (Univ of Rochester) The shortest period reported was two days The great variability in duration of incubation period and the fact that occasionally it was three weeks or longer emphasize the lack of close correlation between the life cycle of the trichinella parasite and the clinical course These observations substantiate the view that symptoms of trichinosis result mainly from accumulated toxemia rather than directly from activities of the parasite during migration in the body

Trichinella larvae begin to reach the host muscles the sixth or seventh day after ingestion of infected meat then require approximately 14 days to grow and develop to the encysted stage During this time they destroy muscle fibers and thereby give rise to products which presumably cause the toxic symptoms Accordingly the time required for appearance of these symptoms depends on the amount of toxic materials produced i e severity of the infection and the host s ability to neutralize their effects The interplay of these two factors accounts for the great variation in length of incubation

For a drug to be useful in treatment of established trichinosis it has usually been assumed that it should act to kill the larvae migrating to or developing in the muscles Such an agent has not been discovered Some consider that this action might be undesirable because of the possible effects of dead larvae acting as emboli If the view is correct that the symptoms of trichinosis are due mainly to a toxic condition therapy directed to combat the toxemia would appear to be the most logical Favorable results with gluco-calcium (Lilly) in three cases reported by Sogemeier might possibly have been due to such a detoxifying effect

(2) Am J Trop Med. 22 313 317 July 1942

Clinical symptoms and signs are well defined Toward the end of the incubation period (5 21, but usually 7 12 days) mild prodromal symptoms appear the disease starts with a chill rarely with a rigor and with fever which gradually increases to about 104 F after 3 or 4 days This temperature level is maintained for about one week with slight morning remissions Usually after 10 days the temperature begins to decrease and drops to normal after 14 days either by lysis in 2 or 3 days or almost critically frequently after a pseudocrisis Pulse rate is increased and blood pressure diminished The general condition is seriously impaired from the beginning severe headache lumbosacral pains restlessness sleeplessness giddiness and tremulous speech are common Still more characteristic are severe prostration and the flushed face hyperemic conjunctivae and peculiar sullen expression which form the drunken look regularly found in typhus and plague Between the third and fourth day rash appears and general condition becomes worse By using a tourniquet the exanthema is visualized earlier as irregular pinkish to bluish rose spots The spontaneous rash consists of three elements roseolar macules or sometimes slightly raised to flat papules of purple to copper color fading on pressure stand on the background of a dusky deep seated vein pattern called the subcuticular mottling After two or three days capillary hemorrhages appear in the center of the macules partly substituting petechiae which toward the end of the second week develop brown stained spots visible for a variable period Simultaneously with pigmentation a moderate branlike desquamation starts which on gentle rubbing comes off in minute scales Location of the rash is also characteristic Starting on anterior axillary folds lateral abdominal surfaces and inner aspects of the arms it spreads to chest back trunk and flexor aspects of thighs and calves In pigmented people it is visible at its best around the umbilicus Neck and face remain free The tongue is dry and tremu

useful purpose Such individuals may be detected by *agglutination tests or by intradermal sensitivity tests* with vaccine diluted 1 60 with salt solution

The experience with 2 145 exposed, susceptible persons indicated that a useful degree of protection was conferred by annual vaccination More frequent vaccination of exposed laboratory personnel gave more convincing evidence of a high degree of protection Individuals who were not completely protected experienced significant favorable modifications in the course of the disease

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TYPHUS

Typhus and Typhus Prevention are discussed by Robert Heilig and V R Naidu[8] (Univ of Mysore) Epidemic typhus is a louse borne highly contagious disease which cannot be communicated by direct contact from man to man The causative organism Rickettsia prowazeki, lives and multiplies in the gut epithelium of the louse and man is infected when the contents of *the intestines of an infected louse are well rubbed or* scratched into the skin Lice do not become infectious until 4 to 7 days after feeding on a typhus patient and invariably die 12 days after their own infection They leave their human host when his body temperature is extremely low or extremely high and convey the infection to persons living or working with the highly febrile dying or recently expired patient Outbreak among soldiers or poor civilians occurs usually during the cold est season when personal cleanliness is minimal and clothing *maximal the optimal conditions for lice Over* crowding favors lice migration and transmission of rickettsiae to more and more human hosts Starvation reduces individual resistance so that infestation leads to infection and the higher the percentage of high febrility or mortality the larger the number of lice compelled to change hosts

(8) A \ ept c 39 686 697 Oct b 194

typhus includes diseases more dangerous to life than epidemic typhus e g Rocky Mountain fever, whereas others such as Indian tick typhus present almost uniformly good prognosis Tsutsugamushi fever exemplifies a malignant mite typhus with mortality up to 40 per cent whereas cases reported from Simla probably belonging to the same vector group exhibit a milder course

The whole typhus group is characterized by the Weil Felix reaction Agglutinins for certain proteus strains appear in the blood of typhus patients toward the end of the first or beginning of the second week. Epidemic louse borne typhus constantly gives a positive Weil Felix reaction for proteus OX19 and does not show coagglutination of any other strain Typhus forms transmitted by rat fleas and by lice (Brill s disease Tabardillo Manchuria fever) and those whose only vector is the rat flea have identical serologic pictures The Weil Felix reaction is predominantly positive for OX19 but coagglutinins for OX2 are usually present Tick typhus presents difficult technical problems Some members of this group such as Rocky Mountain fever and fievre boutonneuse were supposed to give regularly negative Weil Felix reactions until alterations in serologic technic disclosed proteus agglutinins In tick typhus the titer for the different strains is so variable that this group is called the indefinite type agglutinins for all three strains usually being present equally In Deccan and Mysore typhus which probably belong to this type OX2 agglutination is usually predominant over OX19 and OXK. Agglutination of OXK only without any coagglutinins is characteristic for mite typhus all over the world

Highly unsatisfactory methods of treating typhus make strict application of all prophylactic measures imperative especially in wartime This requires rigid delousing measures of all personnel leaving an infected zone and protection with louse-proof garments and

lous and presents a brown furry coat If nursing care is poor, the mouth is fetid and lips are covered with sordes, parotitis and noma develop easily Except in mild cases the second week brings increasing prostration, lethargy, delirium and sometimes signs of cortical irritation, such as muscular twitchings It is difficult to rouse the patient and stools and urine are passed involuntarily More dangerous than these nerve symptoms is toxic failure of the heart and peripheral circulation, characterized by a rapid, thready pulse, which frequently causes death the twelfth to fourteenth day Bronchitis and pneumonia are common and may prove fatal up to the end of the third week The spleen is only slightly enlarged Urine contains some albumin, and suppression may supervene during the second week. Leukocytes are about 14 000 with an approximately normal differential count In some epidemics positive Wassermann reactions are frequent

In favorable cases a sudden turn occurs about the fourteenth day After a 'critical sleep the patient awakes with lower temperature and better pulse and recognizes his surroundings The tongue clears quickly, appetite becomes ravenous and surprisingly short convalescence may restore the patient to full health although the heart needs rest and close observation for some time

The difference between louse borne typhus and the various kinds of endemic typhus is important In epidemic typhus mortality varies between 10 and 50 per cent in different epidemics Prognosis becomes increasingly poor with increasing age being almost hopeless in patients over 50 Typhus epidemics gain in virulence as they persist In the individual case abundance of the rash gives no clue to prognosis but a rash of definitely hemorrhagic character is ominous as are severe cerebral irritation circulatory failure and bronchopneumonia

Among nonepidemic forms rat flea typhus is usually supposed to be harmless but cases resembling epidemic typhus may appear at any time in an endemic area Tick

sites (2) involvement of human beings is in most cases a mere biologic accident and not a necessary phase in the life history of the rickettsial species and (3) when a new host (man) is invaded possibilities of spread by other means than the original arthropod vector may arise, with consequent change in the epidemiologic features of the disease

In accordance with these postulates it is thus seen that endemic typhus is a result of man s accidental intrusion into that almost equilibrated biologic system rickettsia rat flea and rat Endemic typhus in the rat is almost or wholly subclinical and rickettsial infestation is likewise harmless to the rat flea The rickettsia is passed from vector to host and back again neither is any the worse for it and the three species survive indefinitely The mode of human infection is still somewhat indefinite It was formerly thought that the disease was transmitted by the bite of an infected flea however there is growing evidence that in some cases at least the *organisms are inhaled The rickettsiae are excreted* in large numbers by infected fleas and dry flea feces are known to remain infective for long periods Addey has commented on the frequency with which infection occurred among workmen engaged in demolishing old rat infested premises—i e working in conditions under which they would be likely to inhale dust laden with flea excreta

The typhus rickettsia according to Zinsser evolved in the rat and its fleas endemic typhus is the persisting ancestral form of the disease When accidental infection of human beings with endemic typhus occurs any lice they may be carrying will become infected and a classic louse borne epidemic may be thereby initiated Whereas the rat flea is unaffected by rickettsial infestation the infected louse dies in about 10 days This excludes the possibility that the disease could have developed in a louse man cycle

Scrub typhus also called K typhus or tsutsugamushi

masks for those attending typhus patients Prophylactic active immunization is another measure being tried

Epidemiology of Endemic Typhus Fever in the Southern United States According to William R Whitehouse[9] (New Orleans), endemic typhus is known to be continued in rats and spread by rat fleas from rat to rat and occasionally to man although its origin is a matter of speculation It is not known if a patient with endemic typhus may start a louse borne epidemic Only in the last few decades has endemic or murine typhus been recognized as an entity, related, if not identical to Brill s disease The brown rat and tropical rat flea *are mainly responsible for extension of the disease,* although several other potential rodent reservoirs and suitable vectors exist

In the last 15 years incidence of typhus fever in the Atlantic and Gulf states has increased Nearly 60 per cent of the counties in these states reported cases since 1922 of eight southern states South Carolina is the only one which did not show a rise in 1941 over 1940 The fact that endemic typhus has increased in incidence and appeared in new cities far from its earlier habitat indicates its increasing importance as a public health problem rat control becomes of paramount importance Danger of extension of endemic typhus northward to the larger cities where the louse is more common is not theoretical Louse borne typhus is not dangerous as long as the economic *and thus the sanitary status of city and* rural populations are maintained Throughout the centuries typhus has been associated with war famine economic stre s and breakdown of the sanitary dam built against all diseases especially typhus fever

Rickettsial Diseases in Australia In a discussion of the evolution of the rickettsiae F M Burnet[1] (Melbourne) presents three propositions (1) the pathogenic rickettsiae are primarily insect symbionts or semipara

(9) N w O lea M & S J 95 7^33 N embe 1942
(1) M J Aust 1a 2 129 134 Aug 22 1942

exempt The commoner mild types such as mumps, measles epidemic colds smallpox and chicken pox may occur at any age though they are infrequent after middle life Diseases due to neurotropic viruses are infrequent after middle life except those transmitted by tissue abrasions such as rabies

Trench Fever is described by Arthur Hurst[3] This louse borne disease caused by Rickettsia quintana is transmitted to man when an area of skin on which the infected lice have been crushed is scratched The incubation period is 15 25 days Onset is usually sudden without premonitory symptoms but it is occasionally preceded by malaise for one to two days The earliest symptom is a severe headache especially frontal and behind the eyes this is rapidly followed by pain in the lower part of the back and on the second or third day in the legs Neck pain sometimes accompanied by stiffness suggestive of meningitis may occur The patient generally shivers at the onset but there is never a definite rigor He is sometimes flushed and often sweats profusely Nasal or bronchial catarrh is absent Anorexia ensues and the tongue is moist and often slightly furred Mild pharyngitis may exist There is usually no rash but herpes labialis sometimes occurs The shins are always tender even in the absence of the leg pain but there is no muscular tenderness Splenomegaly may occur with the initial pyrexia Leukocytosis is inconstant during the febrile periods

In the brief type of trench fever the temperature rises rapidly to 102 104 F but the pulse rate is only slightly increased On the third or fourth day the temperature suddenly falls to normal or subnormal without corresponding symptomatic improvement After several hours it rises again and then within two to five days again falls to normal on which occasion there is immediate symptomatic relief Sometimes the initial remission does not occur pyrexia persisting for about a week

(3) B t M J 318 3 0 8 pt 12 1942

fever, is another example of a human disease in which man merely blunders into a biologic system with which he is not essentially concerned This infection is borne by a mite (Trombicula) which is widely distributed from Japan to Queensland The vertebrate host varies with the region involved In Japan field mice form the main reservoir and in Queensland rats and bandicoots

Q fever may also be transmitted by infected dust The first cases observed at Brisbane were limited to abattoir workers and the presumptive path followed by the rickettsia from the bandicoot reservoir to the human air borne infections has been traced Q fever infections with a primary pneumonitis have also been frequently observed in laboratory workers substantiating the possibility of inhalation infection

The Rickettsiae and the Pathogenic Viruses are discussed by F A Carmichael[2] (St Joseph Mo) The rickettsiae are diseases due to a group of bacteria like organisms transmitted through parasitic vectors Some are highly pathogenic others relatively innocuous Like many other virus diseases the rickettsiae are characterized by inclusion bodies and it has not been clearly demonstrated whether the virulent factor may be attributed to the specific bacteria like organisms or to virus transmission the organisms being merely a side issue of a status similar to the Negri bodies in rabies

Recent investigations have placed less value on the presence of inclusion bodies as it is believed that these bodies are found in about only 50 per cent of virus diseases Morphologically, there is marked variation in inclusion bodies Those found in herpes chickenpox and yellow fever are apparently morphologically identical while the Guarnieri bodies of smallpox and the Negri bodies of rabies exhibit entirely different morphologic characteristics

While there seems to be a greater susceptibility to virus infections in childhood and early life no age is

(2) J K . M S 44 189 190 J 1943

should be sent to a convalescent depot where fresh air good food and progressive exercise quickly restore him to full capacity

Use of Atabrine in Two Cases of Typhus Fever is reported by Harold Freed[4] (Dallas Tex) Improvement in both coincided with administration of the drug but it is recognized that termination by crisis in the first case and by lysis in the second might have occurred if atabrine had not been used However since atabrine when properly exhibited is relatively innocuous it is suggested that trial be made of it in other cases of typhus fever so that its effect in this disease may be evaluated

In both of these cases the diagnosis of typhus fever was supported by the facts that the blood showed no malarial parasites history and temperature were not characteristic of malaria agglutination tests for undulant fever and typhoid fever were negative and a strongly positive Weil Felix reaction was present This reaction could also occur with Rocky Mountain spotted fever but this condition is extremely rare in the Dallas area whereas typhus is endemic

Typhus Modified Breinl Method for Staining Rickettsiae and Other Inclusions J W Fielding[5] (Univ of Sydney) describes a differential staining method for rickettsiae and other inclusion bodies it is applicable to smears and sections of animal and arthropod material The technic has been divided into series A which includes both fresh and old faded smears and series B which includes sections of vertebrate and arthropod tissue

TECHNIC —*Series A* —For fresh smears the following procedures are carried out (1) Make thin evenly distributed smears and dry them in air (2) Fix them for one minute with acetic Zenker solution (3) wash well with water (4) soak for one minute in 1 per cent potassium iodide solution (5) wash well with water (6) stain for two minutes with Loffler's methylene blue (30 cc saturated alcoholic methylene blue mixed with 1 cc of 1 per cent potassium hydroxide solution in 99 cc

(4) M Bull, V t Admin 19 446 447 Ap il, 1943
(5) M J A t l 1 435-437 M y 15 1943

There is often a single relapse after an interval varying from a few hours to 10 days, but generally less than 4 days, the temperature rises to 100 101 F for 24 to 48 hours during which symptoms return with diminished severity The patient is usually fit for duty almost immediately after the temperature falls again

In the long or periodic, type of trench fever the temperature rises to 101 104 F on the first evening The initial attack is variable in duration the temperature may be normal the first morning, high in the evening, normal the second morning and rather less high the second evening than the first after which it remains down In other cases the first attack may last four or five days the temperature always being lower in the morning than the preceding and following evenings and *reaching its maximum on the second or third day* With the fall in temperature at the end of the initial attack all symptoms disappear After being well for 2 to 10 days, the patient complains of a return of headache and leg pains which culminate at night The temperature rises in the evening to a point that is generally a little lower than the highest temperature in the first attack It falls to normal or nearly normal the next morning and either remains down or rises to a lesser extent the second evening thereafter to remain normal The general symptoms are much less severe than in the first attack but leg pain and tenderness in the shins are usually greater and they may not disappear in the interval between the second and the third attack although the headache which is generally the most prominent symptom during the attack is never present in apyrexial periods Recurrences follow periodically at four to eight day periods, five days being the most common Each succeeding attack is milder than its predecessor

There is no treatment to prevent these recurrent attacks Aspirin is the most effective analgesic *It* is important not to keep the patient in the hospital longer than is absolutely necessary As soon as possible he

tions, flatten and mount sections on slides and dry sections overnight in an incubator at 37 C, and (14) continue as in series B from the sixth step

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WHOOPING COUGH

Pertussis Immunity with Toxin and Antitoxin Jesse G M Bullowa Janet Alterman Nicholas Katona Margaret Scannell and Arthur Robinson[6] (New York Univ) present a study of antitoxin immunity actively induced and passively conferred in well and ill children based on the fact that endo and exotoxin of Haemophilus pertussis are identical and that the toxin is antigenic

Of 135 unselected children living at home 100 were given pertussis toxoid antigen and 35 pertussis vaccine Toxoid was prepared by addition of formol to pertussis toxin and contained 300 units of toxin per cc Vaccine was prepared to contain 20 000 000 000 bacilli per cc Each child was given 2 cc material intramuscularly in the buttock once a week for four weeks The toxoid produced local soreness and induration for one day and fever rarely

As measured in rabbit skin test units blood titers after injections indicated that both toxic and vaccine produce a rise in neutralizing antitoxic antibody The usual initial titer was less than 0 3 unit and the terminal titer 1 unit per cc The fact that vaccine stimulates an antitoxic antibody suggests that part of its antigenicity is due to presence of pertussis toxin There were 10 infants in 1 of whom an increased antitoxic titer developed and in another new born a fall Among the 32 with blood titers analyzed after six months 22 showed a rise in titer Among the 4 who received vaccine and had six month titers all showed a rise Of nine known to be exposed only one child given toxoid has contracted the disease

In children in the active stage of the disease of 11

(6) J A M A 1 0 886 890 N 1 1942

of distilled water), (7) wash well with water, (8) differentiate and counterstain for one half to two minutes, constantly moving the slide in orange tannin solution (3 Gm orange G dissolved in 150 cc of 70 per cent alcohol, mixed with 350 cc. distilled water in which 50 Gm tannic acid has been dissolved) again (9) wash well in water, and (10) dry in air or by blotting with flufless paper

Smears faded after the use of the Giemsa, Castaneda, Archibald and other methods should be decolorized with methyl alcohol and restained by means of the foregoing procedure from the fourth step onward

Series B —For tissue sections (1) fix small pieces of tissue for two hours at 60 C or overnight at room temperature in acetic Zenker solution (2) wash in water and pass to 70 per cent alcohol (3) clear of mercury in iodized alcohol solution, dehydrate clear and embed in paraffin (4) cut section 4 or 5 µ thick and flatten on water at 45 to 47 C (5) mount on slides and dry overnight in the incubator at 37 C, (6) clear off paraffin with xylol and pass through graded alcohols to water, (7) complete mercury extraction for two minutes in 1 per cent potassium iodide solution and wash in water, (8) stain for two minutes with Löffler's methylene blue, (9) wash well with water, (10) differentiate and counterstain for one-half to two minutes by constantly moving the slide in orange-tannin solution, (11) wash well with water (12) pass with constant motion through graded alcohols to xylol, and (13) mount in neutral balsam

The technic for arthropod sections is essentially the same as that for other tissues but the process is slower because the entire animal is fixed stained and sectioned (1) Fix the material for at least 24 hours in acetic Zenker solution, (2) wash well in running water, (3) pass up slowly through graded alcohols to 70 per cent, (4) treat with iodized 70 per cent alcohol for an extended period adding fresh iodine solution if required (5) extract the iodine with 70 per cent alcohol, (6) dehydrate thoroughly (7) use two changes of a mixture of equal parts of absolute alcohol and ether, each for at least 24 hours (8) impregnate for three to seven days in 2 per cent celloidin in alcohol and ether and leave for a similar period in 4 per cent celloidin solution (9) soak for one and a half to two weeks in 6 per cent celloidin in alcohol and ether, (10) transfer with a minimum of celloidin to chloroform and harden for a few hours, (11) impregnate with chloroform and paraffin for 2 hours at 60 C (12) put through two changes of paraffin at 60 C, leaving for 30 minutes in each, (13) embed the animal and cut serial sec-

wall Culture is taken from only one side of the nose To inoculate the medium a drop of 0 85 per cent sodium chloride solution is placed on the surface of Bordet medium near one edge and the material from the swab gently mixed into the solution Streaking is carried out with a flexible platinum loop

Of 438 nasopharyngeal cultures from 248 patients with pertussis and 198 cough plate cultures from 157 patients 52 per cent of the former and 37 per cent of *the latter were positive Of 248 primary nasopharyn* geal cultures 61 per cent were positive as compared with 37 per cent positive of 157 primary cough plate cultures When 183 simultaneous cultures were made by the two methods in 165 cases 57 per cent were posi tive by the nasopharyngeal method and 34 per cent by the cough plate method This difference (23 per cent) was statistically significant The difference was even greater when data obtained by cultures from infants under 3 were analyzed

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CHEMOTHERAPY

Chemotherapy in the Bacteremias Maxwell Finland[8] (Harvard Univ) discusses diagnosis and specific treat ment of patients with a blood stream invasion with the common pathogenic bacteria accompanied by a febrile illness

Diagnosis is established by demonstrating the organ isms in blood cultures made in suitable mediums Meat infusion and hormone broths are satisfactory for culti vation of most common organisms Special mediums or methods are rarely necessary When blood cultures are taken in patients receiving sulfonamides addition of 1 to 5 mg per cent para aminobenzoic acid to the medium may be helpful.

Both presence and identification of the organism in blood cultures are of great significance (1) They aid

(8) C nect t M. J 7 92 100 F bruary 1943

not given specific treatment only 4 had increased anti toxic titer, and 8 others with blood titrations done at varying periods 5 had an increased titer

In an attempt to modify the course by giving vaccine, 9 of 11 had a rise in antitoxic titer after one month, but the disease was little changed In further attempts to determine the effect of a specific agent on the clinical course, 33 sick children were given 6 10 cc toxoid or antigen, and 4 showed a rise in titer at the end of a month, but no clinical improvement was noted

Thirty three children with pertussis were given rabbit antitoxin in 6 to 50 cc doses 8-43 days after onset of symptoms There were no fatalities Nine attacks were severe at onset No decided clinical improvement was noted although in two cases in which antitoxin was given eight and nine days after onset slight improvement was observed

To prevent pertussis 25 exposed children were given antitoxin intramuscularly on alternate days dose varying with age of the child and degree of exposure, with maximum of 10 cc antitoxin given any child The children were observed for nine months during which time incidence of pertussis in the community was high Seventeen of the 25 children remained in family contact with patients to whom they were exposed, even after prophylaxis and of the 25, only 1 contracted the disease

Method of Nasopharyngeal Culture in Diagnosis of Whooping Cough Anne Morris Brooks William L Bradford and George Packer Berry[7] (Univ of Rochester) prepare the swab for culturing the nasopharynx by tightly wrapping a bit of cotton around the end of a piece of flexible copper wire 6½ in long The swab is placed in a pyrex test tube and the tube plugged with cotton is autoclaved Nasopharyngeal culture is taken by gently passing the swab back through the naris until it touches the posterior nasopharyngeal

(7) J A M A 120 883 885 Nov 1 1942

Use of Tyrothricin in Treatment of Infections Charles H Rammelkamp[9] (Boston Univ) describes results in 58 localized infections Satisfactory results were obtained in ulcers infected with Staphyloccus aureus Streptococcus haemolyticus and faecalis Tyrothricin did not affect gram positive organisms when the ulcer contained both gram negative and gram positive bacteria attributed to production of inhibitory substances by the gram negative bacteria One ulcer did not completely heal because the organism became markedly resistant to tyrothricin during therapy Ulcer healing was not retarded by tyrothricin in fact when infection was the primary cause of the ulcer healing was rapid

Application of 22-70 mg tyrothricin at operation on 15 mastoids infected with hemolytic streptococci reduced the number of positive streptococcic cultures postoperatively After more intensive postoperative therapy all streptococci disappeared In these patients cultures made after mastoidectomy usually showed Staphylococcus aureus apparently because insufficient tyrothricin was applied to sterilize the mastoid cavities The results justify further trial of tyrothricin in mastoiditis after operation

No benefit was noted in four patients with empyema given direct injection of tyrothricin before surgical drainage In one patient there was a decrease in pneumococci in the pleural fluid but sterilization of the cavity was not obtained Possibly in patients with streptococcic or pneumococcic empyema treated with somewhat larger amounts of tyrothricin early in the disease the infection may respond Staphylococcic empyema is somewhat more resistant After open drainage of empyema irrigation with tyrothricin suspended in an 0 85 per cent solution of sodium chloride or dextrose may have value in one patient with hemolytic streptococcic

(9) W Med 2 830-846 Septembe 1942

in early diagnosis of some diseases like typhoid fever and meningococcic infections without meningitis (2) Identification of certain organisms directs attention to possible foci of infection When a focus is not demonstrable and does not become apparent during infection, an intravascular focus such as thrombophlebitis or endocarditis should be suspected (3) Isolation of bacteria from the blood stream is useful in prognosis for recovery and for probability that metastatic foci will develop (4) Identification of the organism is important in choice of specific therapeutic agents including the sulfonamides It is indispensable when specific antiserums are to be used

Organisms most commonly cultivated from the blood stream are hemolytic streptococci, Staphylococcus aureus pneumococcus Streptococcus viridans colon bacillus gonococcus meningococcus and Friedlander s bacillus Of sulfanilamide sulfapyridine sulfathiazole and sulfadiazine the last is least toxic and equally or more effective against these organisms There may still be some question whether sulfathiazole is better in gonococcic and staphylococcic infections All are highly effective against the meningococcus Except for sulfanilamide, all are effective against the pneumococcus although the toxicity of sulfapyridine makes its use less desirable Sulfadiazine is definitely the drug of choice in hemolytic streptococcic infections from the standpoint of both effectiveness and low toxicity In staphylococcic and colon bacillus infections sulfathiazole and sulfadiazine are probably equally effective However sulfadiazine can be used more intensively over a longer period and with less danger of toxic effects None of these drugs is highly effective against Friedlander s bacillus although sulfadiazine is probably superior to the others Data on effects of the various drugs on Streptococcus viridans infections are inconclusive

per kg over a five day period Under the same conditions 3 2 Gm per Kg is lethal for some mice The toxic dose of crude penicillin appears to be about 64 times the effective dose as determined by subcutaneous injection in mice On the basis of weight, penicillin appears to be more effective than sulfonamides in streptococcic, pneumococcic and staphylococcic infections in mice It had no apparent effect in experimental infections caused by Mycobacterium tuberculosis, Trypanosoma equiperdum or the influenza virus PR8

[It would seem from many reports that penicill n will be more valuable in staphylococcic infections than any agent yet developed —Ed]

Effects of Sulfanilamide on Smallpox According to S G Vengsarkar, T U Poonen and S A. Walavalkar[2] (City Fever Hosps Bombay), administration of prontosil to a great extent reduces mortality in the confluent and the semiconfluent types of smallpox This reduction is more marked if prontosil is administered early Mortality of 67 1 and 22 7 per cent was obtained in confluent and semiconfluent types respectively as compared with mortality rates of 84 8 and 23 per cent in similar types treated symptomatically Calculation shows that the mortality in confluent cases was reduced 17 1 per cent by early use of prontosil These figures would have been even more favorable if the controls had not been selected late in the epidemic when virulence of the disease was decreasing

Prontosil treated patients present fewer toxic manifestations than do those treated symptomatically This difference is most marked in the confluent type In only 67 1 per cent of the prontosil treated confluent cases were there toxemic manifestations while in 81 8 per cent of symptomatically treated confluent cases there was evidence of toxemia The semiconfluent cases do not seem to benefit in this respect Sulfanilamide administered in the vesicular stage decreases incidence and degree of toxemia and complications and serves

(2) J I di n M A. 11 361 365 S ptember 1942

empyema, sterilization and healing were rapid Tyrothricin irrigation was ineffective in staphylococcic empyema

The value of tyrothricin in other forms of infection has not been established Superficial streptococcic infections of wounds burns or skin should respond to local application, staphylococcic infections are likely to be much more resistant Application of tyrothricin by spray was reported to decrease the number of streptococci in throats of carriers but in one patient with streptococcic pharyngitis, no decrease in organisms was observed One patient with sinusitis due to hemolytic streptococci and Staphylococcus aureus improved after tyrothricin irrigations of the sinuses

No serious toxic effects were noted Application of an alcoholic solution of the active substance to ulcers frequently causes a burning sensation which disappears after two or three applications Injection of tyrothricin into closed body cavities requires caution for in animals large amounts of tyrothricin injected into the pleural cavity caused adhesions and damage to underlying lung parenchyma Large amounts should not be instilled into nasal cavities since some may reach the lungs and cause serious local reaction

Since gramicidin is less toxic than either tyrothricin or tyrocidine and is more potent against gram positive organisms it may prove more useful in treatment of certain localized infections

[It seems probable from reports that neither gramicidin nor tyrothricin is as effective as penicillin.—Ed.]

Toxicity and Efficacy of Penicillin Experiments conducted by Harry J Robinson[1] (Rahway, N J) indicate that crude penicillin is toxic for mice when given intravenously in single doses of 0 5 1, 1 5 and 2 Gm per Kg More highly purified preparations appeared to be less toxic than the crude preparation when compared on a weight basis When given subcutaneously penicillin is well tolerated by mice in daily doses of 1 6 Gm

(1) J Pharmacol. & Exper Th rap 77 70-79 Ja ary 1943

MISCELLANEOUS CONDITIONS

Observations on Cholera Vaccine L E Ranta and C E Dolman[4] (Univ of Toronto) injected heat killed phenol killed and formalin killed Vibrio cholerae suspensions into rabbits The phenol killed vaccine evoked the highest and best maintained O and OH titers Average O and OH agglutinin responses in rabbits to five separate lots of phenol killed cholera vaccine ranged from 1 120 to 1 500 and from 1 1170 to 1 2000 for the O and OH agglutinins respectively Admixture of cholera vaccine with T A.B T occasioned no significant loss in capacity of the mixture to produce typhoid and cholera O and OH agglutinins Administration of cholera vaccine by intravenous and subcutaneous routes in two to three doses at weekly intervals showed that the best average response followed a series of three intravenous injections Agglutinins rapidly disappeared from the blood irrespective of route of administration and number of doses of vaccine

Dengue Fever is reviewed by A S Walker E Meyers A R Woodhill and R N McCulloch[5] (M C, R A A) Dengue fever is a specific fever caused by a filtrable virus conveyed by Aedes aegypti and possibly other mosquitoes occurring usually as a rapidly spreading epidemic Manifestations vary not only from epidemic to epidemic but also during any one given outbreak There are few if any pathognomonic signs or symptoms Incubation period is usually four to seven days Except in mild cases prostration is rapid severe and characteristic True rigors are rare but shivering sensations are usual Prodromal malaise and pain in limbs may be noted for a few hours Soon after onset the patient appears flushed sometimes cyanosed face is puffy with suffused eyes and is curiously dull and

(4) C ad Pub Health J 34 26 37 J nu ry 1943
(5) M. J A at alia 2 3 2 8 Sept. 12 1942

to lower mortality, particularly in semiconfluent cases [As the sulfonamides are generally ineffective against virus infections, their value probably consists in combating the secondary staphylococcic infection in the pustules.—Ed]

Pathologic Lesions Following Administration of Sulfonamides Morris A Simon[3] (Jewish Gen l Hosp, Montreal) describes various pathologic lesions attributed to the sulfonamides in experimental animals and man In the heart, *the lesions take the form of interstitial myocarditis* with occasional foci of necrosis In man blood vessels may show inflammatory lesions indistinguishable from those of periarteritis nodosa in the viscera, in the brain there appears to be injury to the vascular endothelium with associated secondary parenchymal damage Liver lesions are characterized by widespread focal necrosis, and, as part of a general necrotizing process focal necroses may be found in lungs lymph nodes spleen and adrenals The kidneys and urinary tract may be damaged by urolith formation with obstruction and subsequent inflammation In association with agranulocytosis, the bone marrow shows arrest of maturation of the granular series with destruction of the more adult forms, in cases of hemolytic anemia there is erythropoietic stimulation Skin changes are of nonspecific inflammatory nature The sulfonamides act as mild irritants and foreign bodies when placed in serous cavities There is no valid evidence to indicate *that these drugs are capable of producing tumors* Since the lesions attributed to the sulfonamides in human beings have for the most part been reproduced in healthy experimental animals it seems reasonable to conclude that the lesions described in human beings are due to the drugs used rather than to the diseases for which the patients were being treated

(3) Am J M Sc 205 439-454 March 1943

days If benefit does not accrue within this period use of bacteriophage is discontinued Hansraj has also found that colonic irrigations with weak potassium permanganate solutions have good effect. With regard to intestinal antiseptics he has found guaiacol carbonate and salol to be useful Also advocated is the use of liquor hydrargyri perchloridi in 20 minim doses with 1 to 2 minims of oil of cinnamon three times daily

Cardiac stimulants should be used as indicated and intravenous glucose and saline solutions are most valuable in combating the toxemia of typhoid fever

Chronic Melioidosis Melioidosis has been identified in Rangoon Malaya Cochin China and Ceylon In 1932 Stanton and Fletcher analyzed the records of the only 83 cases available including 6 in Europeans in only 9 had diagnosis been made ante mortem All but two died within 20 days of onset It is primarily a disease of rodents but does not appear to be widespread The mode of transmission to man is uncertain but probably occurs through consumption of food contaminated by rodent excreta Case to case infection has not been recorded The causal organism is Pfeifferella whitmori The clinical picture is extremely variable the disease having simulated cholera plague typhoid bronchopneumonia amebic hepatitis and pyelonephritis Thus many unidentified cases must have occurred Like glanders which it resembles this blood spread infection is characterized by formation of multiple infective granulomas almost anywhere in the body It is rarely subacute or chronic Alan Grant and Claud Barwell[7] report a chronic case diagnosed in England

A soldier enlisted in 1934 at 23 and served in Singapore from 1935 to 1938 and on the mainland of Malaya for three months early in 1938 When sent to Penang he was stationed in a rat-infested area but was never bitten In 1937 1938 he had soft chancre cystitis and gonorrhea

The first phase of illness began in May, 1938 when two months after leaving Penang he developed arthritis of the

(7) L cet 1 199 201 F b 13 1943

expressionless Headache lumbar pain and aching and tenderness of eye muscles are usual, photophobia is common Oropharyngeal congestion and herpes labialis are atypical but may occur Pain in body and limbs may be troublesome or severe and persistent Joint pain and even joint swellings are described in some epi demics but actual joint involvement is unusual Musculotendinous pain combined with neuro-encephalopathic manifestations produces restlessness Lymphade nopathy is frequent, but may be absent, splenomegaly occurs rarely Fever is the one invariable sign, it may be intermittent or continuous and usually endures four or five days Absolute or relative bradycardia is usual Rashes are inconstant

There is no specific treatment Bed rest simple anal gesics sedatives when required and sufficient con valescence are all that are necessary Complications are uncommon mortality is extremely low

Treatment of Enteric (Typhoid) Fever is discussed by *Jadavji Hansraj*[6] *In considering the active therapy* of typhoid fever Hansraj believes that a liquid diet is a significant factor in insuring cure The fluid intake should be high Water should be given in large quan tities Milk is tolerated by many patients, and for those who dislike milk buttermilk from which the fat has been removed is a good substitute Tea coffee and cocoa are all permissible Additional nourishment may be provided by egg white liberally mixed with water Fruit juices mixed with glucose and barley water should be given ad libitum All spicy foods should be avoided for they may retard the healing of intestinal ulcers Solid food should not be administered until the temperature has been normal for one week Resumption of a normal diet should be as gradual as possible

A more specific measure in treatment lies in the use of bacteriophage This is beneficial if used early in the disease four ampules are given daily for five or six

(6) Antiseptic 39 455-458 July 1942

The patient has required repeated blood transfusions Different sulfonamides have been used Sulfathiazole caused a fall in temperature for two days but fever returned while he was still taking the drug Sulfapyridine caused the fever to abate but had to be discontinued because of vomiting Sulfadiazine caused an immediate response the temperature falling despite presence of abscesses, only to rise again when the drug was discontinued

Infection probably occurred early in 1938 It is impossible to say whether the first clinical sign of melioidosis was the arthritis which developed in May 1938 or the bronchopneumonia in June 1941 Arthritis was not a feature of previously described cases and if it is taken to mark the start of melioidosis the onset was insidious which again is not characteristic If the arthritis is attributed to the gonococcus or an incidental cause the initial sign of melioidosis would be the bronchopneumonia of June 1941, modified by sulfapyridine which seems to have some activity against melioidosis Recurrence of arthritis at this juncture might have been due to onset of an acute generalized infection This would imply a latent interval of three years between infection with Pfeifferella whitmori and onset of clinical manifestations

Human Infection by Pasteurella Pseudotuberculosis The infrequency but high mortality of this infection and the ease with which the causal organism may be confused with Pasteurella pestis led George A C Snyder and Naomi J Vogel[8] (Spokane Wash) to report a case with recovery presumably the third case to be reported in the United States

Man 41 working on rat infested premises on May 16 had pain in the left sacro iliac joint felt feverish and thought he had the flu Fever continued headache and chills occurred and the sacro iliac pain increased radiating down the back of the left leg to the calf Insect bites and contact with rodents or other animals were denied Examination on May 23 disclosed a dry red pharynx coated tongue blowing systolic apical murmur slight tenderness over the left sacro iliac joint slightly exaggerated knee jerk on the left and blood

(8) N rthwest Med. 4 14 15 Janu ry 1943

right hip, followed in June by arthritis of the right ankle After tonsillectomy in July he was transferred to Gibraltar, in December, gonorrhea recurred but responded to treatment In August and November, 1940, there were recurrences of arthritis in the hip, resolving in four to six weeks after rest and salicylates The second phase started June 1, 1941, after return to England, when acute, bilateral bronchopneumonia was diagnosed by roentgenograms The third day arthritic symptoms in the hip recurred and persisted although the *pneumonia responded to sulfapyridine When seen by the* authors in July, he had irregular evening fever of 99 102.5 F with pulse rate 86 100 The right hip was fixed by muscular spasm the joint area was tender, and there was wasting of the surrounding muscles Roentgenograms showed no joint changes, but two months later slight rarefaction of the joint surface was perceptible There were no other positive findings

On treatment by extension the hip pain rapidly subsided Temperature became normal after 10 days, but fever recurred from time to time with sweating and slight malaise but no other symptoms Aspiration of the hip joint produced a little clear sterile fluid Hip extension was discontinued in October, with full and painless movement of the joint The remittent temperature continued with normal intervals not *exceeding three days All examinations remained negative* except the Wassermann and Kahn reactions which were now positive Despite antisyphilitic therapy the clinical picture persisted and serologic reactions were not negative until May 1942 The pain in the right hip recurred in January, 1942, and shortly thereafter he had pneumonitis in both lower zones and right peroneal palsy, with footdrop which had persisted

Feb 2, 1942, urethrorectal fistula developed and simultaneously brawny swellings began to appear on the left side of the forehead, left parotid and both external malleoli Swelling on the right external malleolus disappeared but in the remaining areas abscesses slowly formed Roentgenograms of the skull showed localized osteomyelitis of the frontal bone with destruction of the outer table There was a similar lesion of the left external malleolus All three abscesses healed after incision and curettage and a gram negative bacillus reported to be Pfeifferella whitmori was isolated from the pus of each The remittent fever continued however and back pain occurred in April Roentgenograms in May were normal, but in July they showed partial destruction of the bodies of the fourth and eighth dorsal vertebrae with a large perispinal abscess

of nausea, and many vomited Pain in the lumbar region and legs was frequent Joint pain was present in about a third and epigastric pain in about a half Diarrhea was found in two cases, but constipation was the rule

The most striking finding was a fine red rash distributed chiefly on the anterior aspects of the legs more predominant over the tibia In one case it was also on chest and abdomen The rash was finer but not unlike that seen in measles It was fleeting remaining only 24-48 hours and usually appeared the fifth day

Acutely ill patients presented dull facies with slight to moderate conjunctival injection and some throat injection Temperature range was 100 6 104 5 F, with relative bradycardia of 55 to 90 Other physical findings were absent Average duration of fever was seven days and most patients were out of bed the eighth day

Leukocyte counts for five acutely ill patients ranged from 6 500 to 11 700 with approximately normal differential counts Blood cultures in 11 cases were negative Agglutination tests for typhoid paratyphoid A and B undulant fever endemic murine typhus and tularemia were negative Stool cultures in 13 cases were negative One case occurred in a laboratory technician handling stools from this outbreak

Convalescent serums were obtained from 22 patients including the technician and studied at the National Institute of Health Agglutination tests were done for tularemia undulant fever typhoid and paratyphoid A and B the Weil Felix test was also conducted using proteus strains OX2 X19 and OXK All such tests were negative

Etiology of Acute Illness among Workers Using Low Grade Stained Cotton was studied by Roy Schneiter Paul A Neal and Barbara H Caminita[1] (U S Pub Health Service)

One hundred and twenty two samples of stained,

(1) Am J P b H lth 3 1345 1359 Dec mbe 1942

pressure 110/90 Urinalysis was negative Blood studies showed 24,000 leukocytes per cu mm Roentgenograms revealed only slight osteo arthritis of the left sacro-iliac joint and haziness of the left psoas shadow May 25 roentgenograms showed an irregular shadow, possibly a calculus or an infectious process at the lower pole of the left kidney May 30, leukocytes numbered 15,500 Further roentgenograms of the lumbosacral area yielded no additional information

He complained of pain in his back and left leg, headache, weakness, chills, sweating and malaise but was not prostrated Temperature was 97 104 8 F, pulse 60 120 and respirations 12 36 There was no palpable enlargement of the liver, spleen or lymph nodes nor any jaundice or cutaneous eruption The only gastro intestinal symptoms were anorexia, moderate abdominal distention and constipation Sulfathiazole was given from May 25 to June 2 and an unknown amount later He left June 5 against advice and without clinical improvement About June 12, spiking temperature began to level off, symptoms subsided and appetite returned July 21, one day after he had returned to work no cardiac murmurs were audible and his only complaint was slight weakness He has remained well so far as is known

Blood samples on May 24 and 30 when the temperature reached 104 F cultured in nutrient broth and in Kracke's blood culture medium, yielded a pure growth of an organism which was not agglutinated by immune serums for agglutinating Eberthella typhosa Salmonella paratyphi or schottmulleri, Shigella dysenteriae or paradysenteriae (polyvalent), Pasteurella tularensis or brucella (polyvalent) but was agglutinated by the patient's serum collected May 29, completely to a titer of 1 500 and partially to a titer of 1 1000 This serum agglutinated one polyvalent Pasteurella pestis antigen almost to 1 10 dilution but failed to agglutinate some others

New Disease Entity (?) C D Bowdoin[9] (Georgia Dept of Pub Health) reports an outbreak of 35 cases of an unusual disease during August 1940 In the seven days preceding onset all patients had been bathing in a little stream contaminated by surface privies and by offal from slaughtered cattle

All patients gave a history of sudden onset with severe headache, predominantly frontal postorbital pain chilliness and sweating Two thirds complained

(9) J M A Georgia 31 437-438 December 1942

of nausea and many vomited Pain in the lumbar region and legs was frequent Joint pain was present in about a third and epigastric pain in about a half Diarrhea was found in two cases but constipation was the rule

The most striking finding was a fine red rash distributed chiefly on the anterior aspects of the legs more predominant over the tibia In one case it was also on chest and abdomen The rash was finer but not unlike that seen in measles It was fleeting remaining only 24-48 hours and usually appeared the fifth day

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One hundred and twenty two samples of stained,

(1) Am J P b He lth 3 1345 1359 Decembe 1942

tinged and normal cotton, cotton dust, linters cotton seed soil, hemp dust and grain elevator screenings were studied Samples of cotton incriminated in outbreaks of illness contained no toxic gases, chemically extractable substances insecticides or pathogenic fungi to which the illness could be attributed. However they did contain a gram negative rod shaped bacterium from 3 000 000 to more than 10 000,000 per Gm It was not isolated from high grade cotton Seventy of 81 samples of materials reported to have caused illness contained the same strain of bacterium as determined by biochemical tests This bacterium is actively motile and encapsulated Its Imvic reaction is — — ++ *it ferments lactose liquefies gela* tin slowly and produces acid and gas in almost all differ ential mediums except adonitol inositol and inulin It has been tentatively placed in the Genus Aerobacter

A heat stable endotoxin like substance was demon strated in filtrates from saline extracts of stained cotton in filtrates from broth cultures of the cotton bacterium and in killed suspensions of the same organism Homolo gous antibodies which were capable of neutralizing or precipitating this toxic substance were produced in rabbits through injections with these materials It is believed that this toxic substance is in the nature of an endotoxin because of its (1) heat stability (2) lower antigenic capacity and (3) increase with age of culture or destruction of cells

The same type of disabling illness could be produced in man by inhalation of (1) dust from normal cotton contaminated with the cotton bacterium and its culture filtrates (2) dust from stained cotton containing a high incidence of the cotton bacterium and (3) a fine mist of a sterile filtrate from cultures of this micro organism The severity of symptoms and physical findings are de pendent on the presence and concentration of the cotton bacterium or its products in the cotton dust inhaled and on the duration of exposure

Intradermal injections of the filtrates of stained cotton extracts and culture filtrates of the cotton bacterium in man resulted in severe inflammatory lesions characteristic of an intoxication rather than a hypersensitivity

The clinical findings developed experimentally in man were the same as those reported in cases of acute illness among workers exposed to high concentrations of stained cotton dust The clinical syndrome of this illness is similar to that of an acute intoxication Since the illness closely resembles mill fever Monday fever and gin fever in cotton mill workers and heckling fever mill fever grain fever and hemp fever reported in workers inhaling flax jute grain and hemp dust respectively, it is suggested that the toxic products liberated by the cotton bacterium or some closely related species may be the etiologic agent for these diseases

The disease developing among workers exposed to stained cotton dust is characterized by sudden onset 1 6 hours after exposure and short duration of the acute phase usually 24-48 hours after exposure The principal subjective symptoms are conjunctival irritation substernal oppresion dryness of the throat generalized aches fatigue headache cough chills fever anorexia nausea and vomiting

GENERAL CONSIDERATIONS

Studies on Air Borne Infection in a Hospital Ward Harriet E Sommer and Joseph Stokes, Jr,[2] conducted preliminary observations on the effect of ultraviolet light on cross infection in two almost identical wings of the infants' ward of the *Children s Hospital of Philadelphia* They were divided into cubicles enclosed on three sides by 7 ft partitions extending to within 4 ft of the ceiling Ultraviolet lights were installed above the entrance to the cubicles of one wing for continuous irradiation Individual gown technic was used by the nurses in all cubicles

Patients with upper respiratory and other diseases were distributed as evenly as possible Swabbings were made of the nasopharynx and throat of all patients on admission of all patients nurses interns and help once a week and of any individual who showed clinical manifestations of a respiratory infection to determine introduction and spread of pneumococcus The criterion for hospital infection was appearance of a new organism in the nasopharyngeal and throat culture not present at least 7 10 days prior to positive findings Reappearance of an organism 14 days after the last positive culture was considered a continuation of the infection

During observation 73 patients were admitted to the irradiated ward and 54 to the control, 55 per cent of the former and 46 per cent of the latter had an upper respiratory infection Of these 27 per cent in the irradiated and 29 per cent in the control wing showed pneumococci Pneumococcic hospital infections were found in 19 per cent of those in the irradiated ward and 33 per cent of those in the nonirradiated ward By typing it was tentatively determined that 7 per cent of patients in the irradiated ward and 17 per cent of those in the nonirradiated ward were possibly infected by the air

(2) J Pediat. 21 569 576 November 1942

borne route since the particular type of pneumococcus was not isolated from any member of the ward personnel but only from other patients with whom there were no close contacts Infection by contact was assumed in 4 per cent in the irradiated wing and 7 per cent in the nonirradiated wing because the corresponding organisms were harbored by nurses attending these patients In 8 per cent in the irradiated wing and 9 per cent in the nonirradiated wing the bacterial infection could not be traced

Three clinical cross infections occurred in the irradiated and four in the nonirradiated ward There was little difference in number of pathogenic organisms isolated from the air of the two wards Of 90 samples taken in the irradiated ward 36 were positive for hemolytic streptococci and of 67 samples from the nonirradiated ward 34 showed similar organisms Pneumococci were isolated from only 1 of 157 samples These facts suggested that irradiation in the experimental ward had some beneficial effect on the air of the nonirradiated control ward because of an open corridor 47 ft. long between them

Certain uncontrollable factors tend to make interpretation of these studies difficult Therefore Werner Henle Harriet E Sommer and Joseph Stokes Jr [3] studied one mode of air borne infection at a time to obtain basic understanding of the routes involved One of the wards of 16 cubicles was evacuated and sealed from other wards Groups of white mice were placed in six selected cubicles and cultures of hemolytic streptococcus of *Lancefield s group C or of the virus influenza A* were atomized in one cubicle Both organisms spread rapidly throughout the air of the ward Ultraviolet irradiation and propylene glycol vapor were compared as air disinfectants

With heavy concentrations of air borne streptococci (over 3 000 cells per cu ft air) most control mice died

(3) J Pedi t 21 577 590 N mbe 1942

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density ' either by increasing ventilation or by reducing the number of susceptibles and the aggregation may thus be rendered safe from epidemic spread of air borne contagion. According to this hypothesis threshold density of susceptibles varies with ventilation The number of susceptibles sharing a given air supply at threshold density defines threshold ventilation and increased ventilation would provide a proportionately larger number of susceptibles with threshold ventilation. Further it has been demonstrated that irradiation of the atmosphere by ultraviolet light is equivalent to an increase in ventilation

Problem of Air Borne Infection according to T J Mackie[5] (Edinburgh Univ) is particularly significant in war medicine The atmosphere is not a natural habitat of micro organisms but fungi and bacteria emanate to it from various substrates in which they flourish While bacteria enter air often in large numbers their stay may be short As dust particles and droplets settle by gravity organisms are removed from the atmosphere with deposition more rapid in quiet than in disturbed atmosphere although air currents in an enclosed space tend to reduce bacterial content as does humidity

The organisms most likely to be found in air are those which can gain access to it from their natural habitats and can withstand drying Among pathogenic organisms which may readily gain access to dust and be distributed by it in air tubercle and diptheria bacilli staphylococci streptococci pneumococci and spores of anthrax anaerobic bacilli (tetanus welchii etc) and various fungi can survive in the dry state for significant periods Brucella may possibly be distributed in dust Gonococci meningococci Pfeiffer s bacillus Bacillus pertussis and pestis and Vibrion cholerae cannot withstand drying for an appreciable period. Typhoid bacilli and other salmonella organisms and dysentery bacilli are probably not distributed in dust

(5) Edinburgh M. J 49 607 627 October 1942

of streptococcic pneumonia and septicemia, while propylene glycol vapor protected them completely and ultraviolet irradiation failed to prevent death only in the cubicle containing the atomizer

With low concentrations of streptococci (200 500 organisms per cu ft air), all mice survived and cultures from the lungs the eighth or tenth day failed to reveal the streptococcus However, that a carrier state had been induced in the animals exposed under control conditions and not in those protected by ultraviolet light barriers was demonstrated by inoculation of the virus of influenza A 8 10 days after exposure to the air borne streptococcus All mice died of influenza but only those of the control group now showed hemolytic streptococci in cultures from the lungs Instillation of sterile broth only occasionally activated the streptococcus in the carrier

Ultraviolet irradiation and propylene glycol vapor were similarly effective in preventing air borne infection with influenza A virus All controls died Propylene glycol vapor protected completely against death and only a few lesions were noted in animals from the cubicle containing the atomizer More lesions and several deaths were observed in the same cubicle when the air was irradiated by ultraviolet lights, and pulmonary involvement was noted also in other locations close to the atomizer under the same conditions

These results indicate that both ultraviolet light and propylene glycol vapor are effective disinfectants of air Their application depends on the individual problems and location to be disinfected. Only infection by droplet nuclei was studied and Flügge droplet and possibly dust borne infections may require different means of control

Dynamics of Air Borne Infection W F Wells and M W Wells[4] (Univ of Pennsylvania) advance the hypothesis that in air borne infection the atmospheric density of susceptibles may be reduced below a ' threshold

(4) Am J M. Sc 206 11 17 July 1943

lack of insight into the basis of these standards principally the numerical relationship between the number of typhoid and colon bacilli in the sewage of a community This ratio is not the same for all communities or for long periods in the same community The community that has had much typhoid fever in the past 20 30 years has a higher ratio of typhoid to colon bacilli than has the community with a low typhoid record The latter therefore may use with impunity a water with a colon bacillus index that would be dangerous for the former The threat of dysenteric infections also appears if the standard is disregarded

The possible role of water in development of other diseases is also important Discovery of poliomyelitis virus in sewage suggested that this disease may be water borne but there has been no outbreak in which epidemiologic evidence even suggests water as a vector to the exclusion of other channels of infection In control of dental caries the fluorine content of water seems to be *significant and before long fluorine may be added to* some waters and subtracted from others with benefit to dental health

Many present milk sanitation measures antedate careful studies of the sources and modes of infection Many milk codes therefore contain items not easily justified They may be defended on the ground that they lead to a low bacterial count yet the emphasis placed on nonessentials is too often at the expense of more significant items Thus in some communities emphasis is placed on barn design or manure pile location disregarding an obvious need for pasteurization Similarly milk from typhoid infected farms is commonly excluded from the pasteurization plant In this it must be considered that if the pasteurization process is inadequate to kill typhoid organisms where they are known to exist and suitable precautions are taken to guard against their introduction into the milk the same process is equally inade

Many viruses have considerable resistance to desicca tion and when discharged from infected persons can survive in air and dust, e g, smallpox, vaccinia, psitta cosis and poliomyelitis, the last of which has been found active in dried material after 24 days Influenza virus can thus survive for weeks if protected from light

For air disinfection the most promising technic is *to introduce into the air a fine spray of a disinfectant* which will kill pathogenic bacteria without exerting a poisonous or irritating action Among such substances are certain coal tar or phenolic derivatives, glycols in cense and smoldering cardboard, but a hypochlorite solu tion yielding hypochlorous acid is most practical. Hypochlorite spraying is easy, and the solution in cer tain concentrations is bactericidal nonpoisonous and nonirritant An instrument of the flit gun type suffices for spraying preferably the baffled gun

Present Epidemiologic Basis of Environmental Sani tation According to Gaylord W Anderson[6] (Univ of Minnesota), establishment of a sound epidemiologic basis for environmental sanitation requires recognition of the intangible esthetic aspects in order that presumed progress through elimination of nonessentials may not later be revealed as retrogression Epidemiology em braces all factors bearing on development and prevalence of any disease condition Consideration must therefore be given to the extent to which disease in the individual or community may be influenced by the environment

Improvement in water supplies needs no justification Ample evidence indicates the relationship between specific contamination and intestinal infection How ever the frequent use by certain communities with ap parent impunity of water that does not conform to accepted standards may suggest that the standards are unnecessarily strict and unjustified by epidemiologic experience To do so would be to display a fundamental

(6) Am J Pub H alth 33 113 119 February 1943

Studies on the Action of Wetting Agents on Micro Organisms E J Ordal and F Deromedi[9] (Univ of Washington) investigated the synergistic effect of synthetic wetting agents on the germicidal action of halogenated phenols Previous data have shown that addition of wetting agents to solutions of phenols at a fixed pH resulted in an increase in the germicidal effect of such solutions Under these circumstances the solutions compared were constant in respect to concentrations of undissociated phenols and phenolate ions On the other hand data in the literature show that addition of wetting agents to unbuffered solutions of phenols may increase or may decrease the germicidal action of such solutions There are several possible explanations of these results Addition of an alkaline solution of a wetting agent such as soap to an unbuffered solution of a phenol will in general result in an increase in ionization of the phenol with a resultant decrease in germicidal activity of the phenol This may be compensated in several ways The wetting agent may possess independent germicidal powers which may compensate for the loss in the germicidal power of the phenol due to ionization On the other hand the wetting agent may enhance the germicidal action of the phenolic species present In particular the wetting agent may increase the germicidal powers of the remaining undissociated phenol or may increase the germicidal powers of phenolate ions and thus compensate for the effects of ionization One or all of these effects may be involved and therefore the resultant germicidal powers of the mixture may be greater or less than that of the original phenol depending on the magnitude of these effects and on the characteristics and proportions of the phenols and wetting agents present

In the present investigation further information was sought concerning the effect of wetting agents on the germicidal action of phenolic compounds In particular

(9) J B ct iol. 45 293 299 M ch 1943

quate to destroy those that enter from unrecognized carriers Epidemiologic experience shows the process to be adequate

Evaluation of Antiseptics and Other Anti Infectious Agents Ward J MacNeal and Nancy C Farnsworth[7] (Columbia Univ) have divided antimicrobial agents into three groups according to their locus of action (1) those acting apart from the human host called disin fectants (2) those acting on the epithelial surfaces or on superficial wounds, designated as antiseptic, and (3) those acting after absorption classed as anti infectious therapeutic agents, chemical and biologic

There is no single easy method of evaluating these agents The method of Ehrlich and Kolle in which large amounts of the agent are administered to animals to ascertain the lethal dose and smaller amounts are given to infected animals to ascertain the therapeutic dose approaches most nearly the ideal procedure The authors are opposed to attempts to evaluate an anti infectious agent on the basis of a single "standard test for the results of such may be misleading Evaluation of an anti infectious agent should be based instead on all available knowledge of its properties obtainable by various procedures

Tissue Permeability and Spreading Factors in Infec tion This contribution to the host parasite problem by F Duran Reynals[8] (Yale Univ) includes consideration of morphologic and functional data on the connective tissue physiologic factors modifying permeability of connective tissues and their influence on infection and resistance, distribution varieties and properties of the spreading factors, spreading factors in infection bac terial spreading factors in infection invasiveness and virulence, the 'critical concentration" of the pathogenic agent in infections and in toxic phenomena and the in fluence on infection of lowering of tissue permeability

(7) J L b & Cli Med 8 963 971 M y 1943
(8) B ct R v 6 197 ᐧ5 D cember 1942.

show that sodium lauryl sulfonate in buffered solutions exerts a definite germicidal effect which is greater at pH 6 0 and 9 7 than at pH 7 7 The solutions containing phenol and sodium lauryl sulfonate show that the presence of sodium lauryl sulfonate exerts a profound effect on the germicidal effect of the phenol at 6 0 This effect diminishes sharply at pH 7 7 and disappears at pH 9 7 At pH 9 7 it appears that the germicidal action of the solution containing sodium lauryl sulfonate and phenol is primarily due to the wetting agent At pH 6 0 the solution containing phenol and 0 1 per cent sodium lauryl sulfonate is more toxic than the corresponding solution containing 0 02 per cent sodium lauryl sulfonate These data show that there exists a synergistic effect of sodium lauryl sulfonate on the germicidal action of 2 4 6 trichlorophenol and that this synergism is primarily with the undissociated phenol

Investigation of the synergistic effect of another wetting agent the dioctyl ester of sodium sulfosuccinate on the germicidal action of 2 4 6 trichlorophenol disclosed that enhancement of the germicidal action of 2 4 6 trichlorophenol at pH 6 0 is even greater than that shown by sodium lauryl sulfonate With both wetting agents the synergistic effect has nearly disappeared at pH 7 7 and at pH 9 7 the solutions with phenol and wetting agents are no more effective than the solutions with wetting agents alone

These experiments indicate that enhancement of germicidal action of a phenol is due to a synergistic effect between the wetting agent and the undissociated phenol rather than between the wetting agent and the phenolate ion To escape the effect of high hydroxyl ion concentrations in the solutions in which phenolate ions predominated 2 4 6 trichlorophenol was selected for these experiments However the data show that the wetting agents themselves exerted a definite germicidal effect at pH 6 0 and 9 7 but were relatively inactive at

an effort was made to determine whether the increase in germicidal action of a solution of phenol by addition of a wetting agent could be attributed to enhancement of the germicidal activity of undissociated phenol or to enhancement of the germicidal activity of phenolate

As a preliminary step, the germicidal effects of o chlorophenol 2 4 dichlorophenol and 2,4,6 trichloro phenol were determined in moderately acid and alka line solutions at 25 C Comparison of the acid and alka line solutions showed that the undissociated phenolic compounds were far more germicidal than their pheno lates though the phenolates were not without toxicity It was possible to compare the germicidal strength of undissociated 2 4 6 trichlorophenol with that of its phenolate without any considerable interference by hydrogen ions or hydroxyl ions The undissociated 2 4,6 trichlorophenol was found to be approximately 100 times more germicidal than its phenolate

Two of these compounds 2 4 6 trichlorophenol and 2 4-dichlorophenol, both stronger acids than simple phenol, were selected for investigation Sodium lauryl sulfonate and the dioctyl ester of sodium sulfosuccinate were selected as anionic active wetting agents of char acteristically different structure These synthetic agents differ from soaps in being soluble in acid and alkaline solutions Staphylococcus aureus was the test organism.

Preliminary experiments were performed to deter mine the most suitable concentrations of the phenols A final concentration of 0 025 per cent was selected for 2 4 6 trichlorophenol and 0 163 per cent for 2 4 dichloro phenol Germicidal tests were performed in solutions at pH 6 0, 7 7 and 9 7

The presence of 0 10 and 0 02 per cent sodium lauryl sulfonate was shown to effect a progressive decrease in germicidal action of 2 4 6 trichlorophenol with increase in alkalinity Tests were made at pH 6 0 7 7 and 9 7 This effect correlates with the decrease in concentra tion of undissociated 2 4 6 trichlorophenol The data

show that sodium lauryl sulfonate in buffered solutions exerts a definite germicidal effect which is greater at pH 6 0 and 9 7 than at pH 7 7 The solutions contain ing phenol and sodium lauryl sulfonate show that the presence of sodium lauryl sulfonate exerts a profound effect on the germicidal effect of the phenol at 6 0 This effect diminishes sharply at pH 7 7 and disap pears at pH 9 7 At pH 9 7 it appears that the germi cidal action of the solution containing sodium lauryl sulfonate and phenol is primarily due to the wetting agent At pH 6 0 the solution containing phenol and 0 1 per cent sodium lauryl sulfonate is more toxic than the corresponding solution containing 0 02 per cent sodium lauryl sulfonate These data show that there exists a synergistic effect of sodium lauryl sulfonate on the germicidal action of 2 4 6 trichlorophenol and that this synergism is primarily with the undissociated phenol

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pH 7 7 It seemed desirable to determine the extent of the synergistic effect between wetting agents and un dissociated phenol in solutions in which the germicidal action which could be ascribed directly to the wetting agents was near a minimum For this purpose, 2 4 dichlorophenol was selected At pH 7 7, 50 per cent of this phenol is undissociated while at pH 9 7 only 1 per cent remains in the undissociated form

The effect of the presence of 0 02 per cent dioctyl ester of sodium sulfosuccinate and of 0 02 per cent of sodium lauryl sulfonate on the germicidal action of 2,4 dichlorophenol in buffered solutions at pH 7 7 and 9 7 were investigated At pH 7 7 a solution containing 0 163 per cent 2 4 dichlorophenol has a definite germi cidal effect This disappears at pH 9 7 where nearly all of the phenol is in the form of phenolate ion The data show that at pH 7 7 the solutions containing wetting agents and phenol are definitely more toxic than those containing wetting agents or phenol separately At pH 9 7 there is a little difference between the solutions with or without phenol, even though the wetting agents are more toxic than at pH 7 7 The data of this experi ment confirm the conclusion that wetting agents en hance the germicidal action of phenols and that this action can be ascribed primarily to a synergistic action between wetting agents and the undissociated phenols

A Study on the Value of a Mixed Bacterial Oral Cold Vaccine is reported by Morris Siegel Marian G Randall Muriel D Hecker and Mabel Reid[1] (New York City) Of 253 persons 125 were given oral cold vaccine capsules while 128 served as controls 147 of the entire group were observed for as long as 210 days For pur poses of immunization a commercial product composed of mixed heat killed bacteria (i e about 25 billion pneumococci 15 billion streptococci 5 billion Haemo philus influenzae and 5 billion Micrococcus catarrhalis per dose) was prepared in capsule form to be taken

(1) Am J M Sc 05 687 69 M y 1943

orally The control group was given placebo capsules of identical appearance Single capsules were taken daily for the first 14 days and twice weekly thereafter as recommended by the manufacturer

Each group had 239 colds during the test period which lasted from Sept 3 1940 through Mar 30 1941 Among those with three or more colds in the preceding year fever colds were reported during the test period by 54 of the inoculated and 48 of the controls Among those with less than three colds the year before more colds were reported during the period of observation by 16 of the inoculated and 7 of the controls The number of colds per person period of observation during the test period was 2 1 for those receiving the vaccine and 2 2 for the controls It was slightly higher for the inoculated than for the controls among those with less than three colds in the preceding year and slightly lower for the inoculated than for the controls among those with three or more colds in the preceding year

Average duration of symptoms in the group taking the vaccine was 10 5 days per cold as compared with 9 7 days for the controls On the whole the duration of symptoms was longer than that reported in most other studies partly because symptoms were recorded daily and partly because symptoms recurring within a period of less than seven days were not attributed to a new cold but to the old one

About 33 per cent of the persons in each group had no absences An additional 25 30 per cent were absent from one to two days and about 15 20 per cent from three to four days In all 80 per cent of the inoculated and 76 per cent of the controls were absent from 0 to four days during the period of observation About 13 per cent in each group were absent from 5 to 7 days and 8 per cent from 8 to 21 days The distribution of inoculated and control persons according to the number of days absent was therefore fairly parallel over the range from 0 to 21 days which included all of the

inoculated and 98 per cent of the controls Three controls (2 per cent of the group) were absent 25 40 and 43 days respectively They increased by 30 per cent the number of absent days in the control group and raised the arithmetic average for the group to 4 2 days per person period of observation as compared with 3 1 for the inoculated On the other hand the median values for the groups were 2 and 2 2 absent days respectively, for inoculated and control individuals

About 40 per cent of the illnesses in each group appeared to be uncomplicated head colds and about 60 per cent were somewhat more severe or associated with complications The cases with complications or which were considered more severe than a head cold were fairly evenly distributed between the two groups

[Cold vaccines are in wide use and owing to ease of administration oral vaccines are more popular than those given subcutaneously This careful study is most important as it indicates that the oral vaccine is of no value In our own experience subcutaneous vaccines are also of doubtful value —Ed]

Species of the Tribes Mimeae Neisserieae and Streptococceae which Confuse Diagnosis of Gonorrhea by Smears are described by George G De Brod[2] (Washington D C) From 147 cases, including 41 patients with purulent conjunctivitis 49 with vaginitis and 57 clinically normal individuals, Mimeae were isolated 45 times gram positive diplococci which tended to lose their stain 6 times and Neisserieae excluding the gonococcus 8 times Neisseria gonorrhoeae were isolated from 10 of 41 patients with purulent conjunctivitis and from 5 of those with vaginitis Thus in 59 cases real or apparent gram negative diplococci were present which could be easily mistaken for Neisseria gonorrhoeae It is concluded that identification of Neisseria gonorrhoeae by smears in conjunctivitis or vaginitis is not justified

Physical Factors Concerned in Inflammation Realizing that bacterial spread is a corollary of the growth

cycle of bacteria and therefore stimulates inflammation Carroll J Bellis[3] (M C U S A) investigated the rates of spread of various bacteria and the factors governing the spread in experimental animals In the rat it was found that tetanus toxin has a spreading factor so powerful that sufficient quantity for lethal issue may diffuse into the general circulation in 10 to 20 minutes after subcutaneous injection In the rabbit Streptococcus viridans Staphylococcus aureus pneumococcus type I and Bacillus coli spread rapidly while Bacillus prodigiosus and pyocyaneus and some strains of Staphylococcus aureus spread slowly in the subcutaneous tissues In the rat determined by the dye method Staphylococcus aureus and albus Streptococcus haemolyticus Bacillus pyocyaneus and prodigiosus and pneumococcus type I have mild spreading factors but Clostridium welchii has a relatively powerful spreading factor In evaluating these last results it should be recognized that the rat is quite resistant to any bacterial growth

Studies of the action of bacterial filtrates on plasma clots disclosed that although Staphylococcus albus produces an exotoxin and leukocidin it does not usually have a powerful spreading factor The staphylococcus may be dermonecrotic hemolytic or lethal. The relative production of coagulase or fibrinolysin may determine whether a patient will live with a boil or die of staphylococcemia Streptococci appear to form a great deal of fibrinolysin this compares well with the rapid spread of streptococci in living tissues

Pathogenicity of Bacteroides Melaninogenicus and Its Importance in Surgical Infections Charles Weiss[4] (Mount Zion Hosp San Francisco) presents evidence that Bacteroides melaninogenicus should be regarded as a significant pathogen in surgical infections He has isolated it in combination with other aerobic and an

(3) Surgery 13 696 72 M y 1943
(4) Ib d., pp 683-691

aerobic bacteria from 45 surgical cases representing various infected wounds and lesions of the pleura and peritoneum and the gastro intestinal respiratory and genito urinary tracts Others have cultivated it from the blood stream during puerperal infection

Experimentally the organism has been shown to possess a fibrinolysin which permits it to dissolve human blood fibrinogen, thus interfering with one of the essential defense mechanisms of inflammation local fixation of micro-organisms In cultures it produces a putrid foul odor and together with the anaerobic Streptococcus putrificus is responsible for the unpleasant odor of some types of pus

Strains of Bacteroides melaninogenicum recovered from human lesions were pathogenic for rabbits and mice Intradermal injection produced in the former intense local inflammation dermonecrosis and occasionally death Previous damage of the tissue by a bacterial toxin enhances the dermonecrotic properties of the organism

Specificity of Lecithovitellin Reaction in Diagnosis of Gas Gangrene Due to Clostridium Welchii Lyle A Weed Sherman Minton Jr and Eunice Carter[5] (Indiana Univ) found that this reaction is not specific for Clostridium welchii or its toxin Many anaerobes likely to be found in an open wound give turbidity and flocculation with lecithovitellin which grossly appear identical with the reaction produced by Clostridium welchii This reaction whether produced by filtrates or supernatant fluids from cultures of aerobes or anaerobes can be inhibited by the monovalent antitoxins for Clostridium welchii and tetani and Vibrion septique It can also be inhibited by such nonspecific materials as normal human serum and M/10 phosphate buffer (pH 7) The reaction is not due entirely to Clostridium welchii toxin (when this organism is used) since the material still reacts after boiling for one

(5) Wa Med 2 95 959 N vembe 194

hour which would destroy any toxin present the material does not react when toxin is neutralized to pH 7 4 which does not destroy lethal and hemolytic factors and cultures grown in a casein medium give rapid and marked reactions with lecithovitellin even though they lack lethal and hemolytic factors Casein broth alone will give the reaction when acidified to a degree comparable with that developing in most welchii cultures Many factors may cause a positive lecithovitellin reaction and certainly some substance in uninoculated casein broth and most lots of chopped meat broth will under certain conditions cause a grossly similar reaction In any event it is erroneous to attribute a positive lecithovitellin reaction to the toxin of Clostridium welchii The reaction is probably due to some substance normally present in broth which reacts only when pH is lowered sufficiently the rapidity and degree of flocculation being almost directly proportional to the degree of acidity

Epidemiologic Aspects of Food Borne Disease are reviewed by Vlado A Getting[6] (Harvard Univ) In food infections the incubation period varies from six hours to two weeks with characteristic averages for the different types of organisms In an investigation of any suspected food borne outbreak an analysis of the symptoms will often give a clue to the etiologic agent The shortest incubation periods are observed in some types of chemical food poisoning where symptoms may occur in 10 minutes to several hours The enterotoxin of Staphylococcus aureus produces symptoms in 2 6 hours whereas salmonella infection incubation averages 6 24 hours Nausea or vomiting is not likely to occur in food infections with long incubation periods

After recording the symptoms of all the patients in a given outbreak the next most important step is to obtain a dietary history from each As soon as the foods which are common to all cases have been deter

(6) N w E gl d J Med 6 54 76 J 10 1943

mined, steps should be taken to prevent further cases Thereafter a study of the vehicle can be made determining its source, handling, storage and preparation in an endeavor to ascertain the mode whereby the food became contaminated Lastly, the etiologic agent is determined by laboratory examination of the food and of the vomitus and feces of patients and food handlers

Diseases of the Chest
(EXCEPTING THE HEART)

J BURNS AMBERSON Jr MD

PART II

DISEASES OF THE CHEST

PHYSIOLOGY—NORMAL AND ABNORMAL

Proper understanding of disease and its management depends on a knowledge of the involved physiologic mechanisms and their disturbance The following articles describe some of the important work accomplished in this field —Ed

Pulmonary Insufficiency in its various forms is discussed by P H Rossier and H Mean[1] (Zurich) In the lung carbon dioxide elimination and oxygen intake are related to such an extent that a definition of pulmonary insufficiency can be based in part on either of these functions The authors believe that this definition should be drawn primarily from the study of the oxygen and secondarily from that of carbon dioxide The latter is complicated by the direct participation of carbon dioxide in establishment of acid base equilibrium Thus actual pulmonary insufficiency is defined as any disturbance of the pulmonary or bronchial function leading to a lowering of oxygen saturation in the arterial blood leaving the lung In addition to this actual insufficiency there are degrees or precursors of this state designated as potential or latent insufficiency which consists simply of a diminution of the functional capacity of the lung The possibilities for adaptation are diminished but the remaining function is more than sufficient to support the needs of life at rest This state can be investigated then by increased functional demands A lowering of vital capacity in a disease such as emphysema for example with normal arterial blood indicates this type of dysfunction The final proof of this state is to increase the threshold of functional necessity to such a point that

(1) Schw z med Wchnsch 73 327 332 M 13 1943

manifest or actual insufficiency appears Actually the difference between real and potential insufficiency de pends merely on the difference in conditions, increased demand renders manifest an insufficiency that remains latent at rest

This definition of pulmonary insufficiency implies that the function of the lung should be studied from two viewpoints, that of the arterial blood to determine mani fest insufficiency and that of spirometry to establish the functional capacity Proof of work, or ergometry, is not *considered here Study of the arterial blood and of spi* rometry allows establishment of the physiopathology of alveolar function and estimation of the important mech anism of defense by the organism The important char acteristics of alveolar function are (1) the quantity of air passing per minute through the pulmonary alveoli or pulmonary ventilation (2) the quantity of oxygen *taken up by the blood for each liter of air ventilating* the alveoli i e alveolar utilization, and (3) the pressure of oxygen prevailing in the alveoli These values can be determined indirectly

The scheme for investigation of pulmonary function includes the spirometric tests of potential function, in cluding maximum respiratory count vital capacity, con sumption of oxygen production of carbon dioxide and respiratory quotient The tests of actual function in clude determination of the pH of the plasma, carbon dioxide content oxygen capacity and oxygen saturation (per cent) of the arterial blood From these values, the ventilation oxygen and carbon dioxide pressure and total utilization of oxygen in the alveoli are calculated

In addition to true pulmonary insufficiency, there are two types of pseudo insufficiency one encountered in febrile diseases and one a more complex mechanism which is secondary to a circulatory short circuit at the level of the lungs Diagnosis of the latter is made by three methods Study of the arterial blood may show changes while spirometry indicates hyperventilation

analysis of alveolar air shows carbon dioxide tension lower than that in the arterial blood and oxygen therapy is incapable of restoring to normal the content of oxygen in the blood

This concept and classification of pulmonary insufficiency aids in solution of many clinical problems both diagnostic and therapeutic encountered in management of patients with chest diseases

[The abstract alone cannot do justice to the conceptions of the authors which should be studied in the original —Ed]

Respiratory Disturbances in the Newly Born Infant are reviewed by Edith L Potter[2] (Univ of Chicago) In the normal infant respiration is initiated a few seconds after birth If the infant does not breathe immediately inhibition is usually due to a pathologic state induced by disturbances in the intra uterine environment or by the processes of labor and only rarely by abnormalities of the fetus itself The conditions which may decrease the oxygen available to the fetus while it is still within the uterus and which may be sufficient to cause its death or which may be sublethal and injure without killing are (1) those which decrease the oxygen in the maternal blood cells (severe anemia poisoning producing methemoglobin and effects of gaseous anesthetics) (2) those which decrease the amount of the circulating maternal blood (shock and hemorrhage) (3) those which interfere with the circulation of maternal blood within the placenta (premature detachment and massive infarction of the placenta) and (4) those which prevent passage of the fetal blood through the cord (prolapse entanglement and hematoma of the cord)

During birth anoxia may be produced by any of these conditions and in addition by trauma which causes intracranial hemorrhage and produces injury to the respiratory center Following birth the initial establishment of respiration may be inhibited or breathing may

( ) Ill n is M J 83 100 107 Febru ry 1943

subsequently become arrested either from late effects of previously induced anoxia or from conditions intrinsic in the fetus and functioning for the first time after birth The respiratory center in the brain may be inadequately developed as a result of prematurity or malformation Conditions primary in the pulmonary tree which may inhibit or alter respiration are (1) malformations including cartilaginous obstruction of the trachea and hypoplasia of the lung (2) occlusion from aspirated debris either as a result of plugging of the trachea or bronchi or filling of the alveoli (3) occlusion from material extruded into the alveoli as from leukocytes and fibrin in pneumonia or pulmonary hemorrhage in anoxia (4) rupture of alveoli during artificial resuscitation with consequent collapse of alveoli from bullous emphysema or pneumothorax (5) incomplete development of the alveoli The most common cause is immaturity of the lung parenchyma If birth occurs before a capillary bed has been produced which is sufficient to permit oxygen-carbon dioxide exchange at a rate which will allow for maintenance of body processes death will inevitably ensue Conditions which may prevent alveolar expansion by external pressure are pneumothorax diaphragmatic hernia pleural or peritoneal effusion excessive cardiac hypertrophy and polycystic kidneys

In addition there is *one* syndrome not commonly recognized which is most common *following* birth by cesarean section The infants usually breathe spontaneously and appear normal for a few hours Subsequently respiratory distress gradually appears Costal retraction irregular or shallow breathing cyanosis muscular twitching and even convulsions may occur The infants usually survive but when death follows the only pathologic lesion observed in most cases is an increase in cerebrospinal fluid within the subarachnoid space around the brain

Respiratory Failure in Acute Poliomyelitis is dis

cussed by Conrad Wesselhoeft[3] (Harvard Univ) In creased interest in treatment of acute poliomyelitis awakened by the Kenny technic has resulted in some confusion regarding the value of the respirator in the presence of respiratory failure in this disease

In spinal poliomyelitis only one side of the diaphragm may be affected and a patient may seem to be getting along fairly satisfactorily with apparently a complete unilateral absence of contractions A patient may also appear to be breathing satisfactorily with only the diaphragm and little use of either thoracic or abdom inal muscles Indications of impending failure consist of visible loss of action in the muscles of normal inspira tion with overaction of the sternocleidomastoid (neck breathing) and other accessory muscles Breathing is at first shallow and later labored Speech is interrupted by inspirations so that the patient can count only to two or three before breathing in Coughing becomes ineffec tive and then impossible Cyanosis implies anoxemia with lowered resistance to the infection as a whole as well as loss of muscle strength When all inspiratory effort is apparently on the point of exhaustion and the expiratory muscles appear to be attempting to compensate with a low vital capacity of air in the lungs the need of a respirator is imperative The ideal time to put the pa tient in is at the first signs of failure delay results in fatigue and anoxemia and may mean the difference be tween death and recovery The patient should be weaned from the respirator as soon as possible Ability to cough is a good indication for removal The respiratory muscles can be alienated from control of the respiratory cen ter as definitely as the leg muscles can be alienated from the cortex by prolonged immobilization in a splint In complete and irreversible paralysis of the respira tory muscles life can be maintained only by continued use of the respirator However there is no way of telling

(3) New E gl nd J M d 8 225 30 Feb 18 1943

at the beginning of muscular failure how much nerve damage is actually taking place That there is a high death rate from respiratory infections following use of the respirator is no argument against its use since this is also true after intubation and tracheotomy

The rate of the machine is not so important as the height of negative pressure Once inside the apparatus, the patient promptly adapts himself to its rate The rate used for children is usually between 20 and 30 per minute, for adults, 15 20 Too great negative pressure injures the alveoli of the lungs and thereby induces pneumonia Children under 10 years should be started at a pressure of 10 cm on the water manometer and this should never be allowed to rise above 14 Adults can be started at a pressure of 12 to 14 cm and there is rarely any reason for allowing it to rise above 16, and never above 20

Respiratory paralysis in poliomyelitis may also be caused by disturbances in the respiratory center itself or indirectly through injury to cranial nerves that control swallowing When the respiratory center is impaired respiration becomes irregular and jerky this is not overcome by the respirator The function of deglutition is vital to respiration in keeping the upper respiratory tract clear when it is impaired choking and finally drowning in mucus occur This condition is combated by atropine gentle suction to the pharynx and most effectively by postural drainage With the foot of the bed raised 2 ft enormous quantities of mucus—a pint or more—will run from the nose and mouth

Although the respirator is useless and even dangerous in respiratory embarrassment due to bulbar poliomyelitis the patient may have a combination of spinal and bulbar involvement with the former sufficiently severe to warrant a trial of the respirator, provided precautions are taken against the effects of the bulbar paralysis

Use of the respirator is fraught with many discouraging experiences Some are due to the types and com

plications of the respiratory failure but others result from the overwhelming damage brought about by progress of the disease Nevertheless numerous patients have obtained comfort relaxation and sleep at a critical period of respiratory embarrassment which saved their lives The respirator is too frequently used where it is not indicated and where it is indicated there often is too much delay Unqualified disparaging statements regarding the value of the respirator increase these delays The Kenny method has much in its favor but as yet no proof has been offered that hot packs can replace the respirator in treatment of the spinal type of respiratory failure in poliomyelitis

Postural Changes in Respiration under conditions of graded hydrostatic handicap to circulation were studied by Elizabeth Brogdon Franseen and F A Hellebrandt[4] (Univ of Wisconsin) The hydrostatic handicap was graded by use of a tilting board It was nullified by suspending the subject from the head and shoulders in a 180 gal. tank of water The full effect of gravity was observed in supported standing with the subject immobilized and in unsupported standing during which free movement above a stationary base was allowed as dictated by involuntary postural sway The respiratory response to protracted support in a critical position was investigated at 75 degrees from horizontal the subject leaning against the tilting table

Respiratory changes induced by posture alteration were out of proportion to concomitant metabolic increases as verticality was approached Respiratory behavior is shown to be closely related to cardiovascular competence It is augmented as the gravitational handicap to circulation is made greater and approaches normal when the compensatory action of postural sway reduces that handicap With suspension in water respiratory behavior approximates that in horizontal position indicating that the vertical position alone has no in

(4) Am J Phy i l 138 364 369 J u ry 1943

fluence on ventilation With few exceptions both fainters and nonfainters responded with some augmentation of ventilation to protracted support in near verticality The increases observed were in many cases due to rises in rate with reductions in amplitude The augmented ventilation seems to be a reflection of the general slowing of the circulation in which the medullary centers are more or less seriously deprived of oxygen unless more effective compensatory mechanisms combat the pull of gravity on the blood column Of these, rhythmic squeezing action of muscle is of great importance

Influence of Abdominal Binders on Lung Volume and Pulmonary Dynamics The lung volume its subdivisions and related aspects of pulmonary function

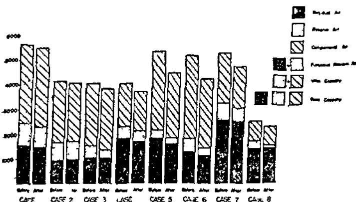


Fig 1 —Cha ges in pulmona y f nct on c used by appl tion of abdom nal b nd s

were studied by M D Altschule and N Zamcheck[5] (Harvard Univ) in six normal subjects and two patients with pulmonary congestion before and after application of abdominal swathes of varying degree of tightness It was found that functional residual air composed of reserve and residual airs, complemental air, volume of vital capacity and of total pulmonary capac

(5) Arch Surg 45 140 144 July 1942

ity and tidal volume decreased and the respiratory rate increased in normal subjects according to the degree of constriction Patients with pulmonary congestion showed evidence both by the measurements of this study and by clinical observations of greatly increased dyspnea and a greater degree of respiratory embarrassment than normal subjects as a consequence of abdominal constriction

The decrease of functional residual air implies a corresponding degree of pulmonary collapse and suggests that binders favor the occurrence of postoperative atelectasis It also indicates that abdominal constriction causes a decrease in negativity of the intrapleural pressure It was found that tight abdominal binders i e as tight as the usual postoperative binders cause decreases in functional residual air of 330 to 375 cc Christie and MacIntosh found that the negativity of intrapleural pressure decreased 2 3 cm water when functional residual air diminished 200 350 cc Decreased negativity of intrapleural pressure impedes peripheral venous return Abdominal binders may also impede venous return from the legs by compressing the great veins of the abdomen These factors are clearly important as contributory causes in the genesis of postoperative shock and phlebitis The decrease in complemental air or limitation of tidal expansion due to tight abdominal binders may give rise to fatigue of the respiratory center and anoxemia resulting in respiratory arrhythmias including Cheyne Stokes respiration the occurrence of such arrhythmias was noted in the present study

[*Another important consequence of abdominal constriction is* interference with the explusive force imparted to the lung by breathing and coughing stagnation of secretion exudate and transudate is favored creating conditions favorable to development of pneumonia The effects of constriction are obviously somewhat counteracted when the patient assumes a nearly vertical position —Ed]

Volume of Air Moved by Artificial Respiration in Anesthetized Men was investigated by D R Hooker

W B Kouwenhoven and J Arthur York[6] (Johns Hopkins Univ) The pole top method of artificial respiration has been designed for men servicing electric power lines who may have "electric shock" and respiratory paralysis as the result of contact with a high voltage circuit The method is applied by a fellow worker who, supporting the victim on his own safety strap in the trunk vertical position spreads his hands over the lower part of the abdomen and makes vigorous rhythmic upward lifts, thus forcing air to be expired In an earlier study made on *conscious men it was found that the volume of air moved* by the pole top method when applied to subjects in the trunk vertical position is somewhat greater than that moved by the Schaefer method as applied to the same subjects in the prone position In the present study the observations were repeated on anesthetized subjects to avoid the possibility of co-operation

The data obtained on three subjects when conscious and unconscious indicate that (1) more air is moved in the unconscious (anesthetized) than in the conscious subject with each (artificial) respiratory act (2) the modified Schaefer method (hands allowed to slip off at the end of each pressure stroke) is superior to the original *Schaefer method (3) the pole top method is an* adequate and valuable procedure (4) it is more efficacious in the trunk vertical position than the Schaefer method in the prone position

Resuscitation in Advanced Asphyxia Role of Positive and Negative Pressure Samuel A Thompson George L Birnbaum and Eugene Ostrow[7] (New York Med College) produced asphyxia in dogs either by mechanical means or by inhalation of inert gases Four methods of resuscitation were used (1) Manual artificial respiration with oxygen was successful in 55 per cent of the experiments (2) rhythmic inflation with oxygen at 12 to 15 mm Hg pressure in 78 per cent, (3) rhythmic

(6) *Am. J Physiol.* 137 649 652 N vembe 1942

(7) Surgery 12 284 ?93 August, 194

suction with oxygen at 8 to 12 mm Hg pressure in 80 per cent and (4) rhythmic inflation and suction with oxygen in 95 per cent

The value of resuscitation alone without the stimulating effect of oxygen can be demonstrated by attempting resuscitation with an inert gas instead of oxygen The authors have called this the phenomenon of asphyxial resuscitation It can be produced in a high percentage of instances only with the combination of inflation and suction This phenomenon cannot be produced after double vagotomy except when oxygen is used instead of nitrogen or other inert gases In this instance resuscitation is accomplished by the factor of oxygen alone and without the benefit of reflex stimuli

To the objection of Henderson and Turner who consider the suction phase of resuscitation as unnecessary in operative asphyxia when the chest is open and the lung is collapsed the authors point out that the noncollapsed contralateral lung is the one on which the benefit from reflex resuscitation depends and that in addition the suction phase maintains a more regular pulmonary ventilation even in the collapsed lung

The Respiratory Phenomenon of Cheyne Stokes is discussed by Otto Klein[8] (La Plata Argentina) This is a definite form of periodic respiration characterized by four phases apnea ascending respiratory phase maximal hyperpnea and descending phase It has been encountered in various conditions especially in those accompanied by disturbances of cerebral circulation in cardiac insufficiency in morphine barbiturate and carbon monoxide poisoning and it can be produced experimentally with hypophysin It also may occur under physiologic conditions e g in hibernating animals in old people in arteriosclerotics and during sojourn in high altitudes The complete phenomenon cannot be produced experimentally after injury to certain parts of the mesencephalon or the thalamus it may be produced by

(8) S m a méd 49 1445 14 3 D 17 1942

traumatic, thermal or mechanical stimulation of the medulla oblongata The most plausible theory concerning the origin of the phenomenon had been advanced by Haldane and Douglas Meakins and others who contend that Cheyne Stokes respiration results from an anatomic or functional lesion of the respiratory center caused by three factors diminution of carbon dioxide anoxemia or asphyxia of the respiratory center and slowing of the general circulation the last being the most important if not the decisive one

Treatment of Cheyne Stokes respiration aside from treatment of the underlying cause should be directed mainly toward remedying the lagging circulation The drug of choice is strophanthin which besides its favorable action on the circulation improves diffusion and utilization of oxygen Of the respiratory stimulants theobromine euphylline deriphylline etc are effective probably through dilatation of the cerebral vessels Camphor coramine and cardiazol have only a brief effect Lobeline owing to its intense stimulation of an exhausted respiratory center may have harmful results The most effective treatment of Cheyne Stokes respiration consists of breathing a mixture of gases i e, oxygen plus 2 5 per cent carbon dioxide The latter has a fourfold effect it has a carbogenic action dilates the cerebral vessels accelerates the circulation and in raising the acidity of the blood increases ventilation According to Ellias of Vienna acid salts have a similar effect He advocates administration of sodium monosulfate (100 Gm or more) Lumbar puncture may be beneficial in cases of cerebral edema Excellent results have been reported by Kratschmer of Vienna who treats Cheyne Stokes respiration with injections of histamine

Conception of Neuralgic Chest Pain is presented by T G Heaton[9] (M C R C A) Among 341 consecutive patients referred to an army medical consulting clinic 100 complained of chest pain and in 53 of these

(9) Canad M A J 47 535 540 December 1942

the pain was a major if not the chief complaint Diagnoses in these 100 cases were psychoneurosis 58 per cent lower respiratory tract disease 22 per cent intercostal neuralgia 16 per cent Other diagnoses were subnormal mentality rheumatic disease malnutrition and convalescence organic heart disease spinal disease or injury and functional dyspepsia Psychoneurosis includes all cases of functional nervous diseases such as anxiety states reactive depression hysteria and all cases to which the term effort syndrome was applied The pain seemed to be of the same character in all the groups listed except that in the small group of spinal disease or injury it was felt more commonly posteriorly or posterolaterally instead of anteriorly or anterolaterally as in the other groups The pain was described as short stabbing with a prolonged dull ache in the same area either alone or between the sharp pains It was characteristically and usually provoked by reaching up stooping over rolling in bed and was aggravated by deep breathing and cough but never as in pleurisy by quiet breathing It was less often provoked by running marching or walking up and down steps It was usually located below the third rib was never substernal was more often on the left than on the right side and occasionally was bilateral In most cases electrocardiographic and x ray examinations were negative

Heaton believes that the pain is based chiefly on over appreciation of an overexcitable pain mechanism and should be termed neuralgic The same pain may occur in apparent absence of the aforementioned conditions and as shown by the other 241 cases any of these conditions may exist without this type of pain The pain in chronic pleuritis effort syndrome and some cases of organic disease of heart and lung cannot be differentiated from these neuralgic pains They are commonly misdiagnosed as pleurisy or heart disease and when the same type occurs in the abdomen as appendicitis or kidney trouble Prognosis varies greatly being worst in psychoneuritis

The pain is sufficiently severe on rare occasions to constitute a moderately serious disability in itself

Erythrocytes and Hemoglobin Values in Acclimatization Produced by Discontinuous Anoxia were studied by J Clifford Stickney and Edward J Van Liere[1] (West Virginia Univ) There has been considerable controversy as to whether or not aviators show definite signs of acclimatization Since aviators spend but relatively short periods aloft they are, of course subjected to discontinuous anoxia The authors also felt that it would be of interest to find a threshold value, i e, how long it would take an animal subjected to a given degree of anoxia for a certain period each day for distinctive signs of acclimatization to develop

Five dogs were subjected to a lowered barometric pressure daily for 6½ hours each day The simulated altitudes to which they were exposed ranged from 12,000 to 18 000 ft (corresponding to barometric pressure of 483 to 379 mm Hg respectively) The experiments were performed for about six months All the animals showed a noticeable increase in number of erythrocytes and amount of hemoglobin. Hemoglobin was first to show an increase Two dogs exposed to a simulated altitude of 12 000 ft showed a distinct increase in the third week. This represents approximately a threshold value as shown by Armstrong and Heim in human beings The first distinct increase in erythrocyte count did not occur before the fifth week. A uniformity was noted in the rise of the red blood count during the experiments After the animals had been exposed to a simulated altitude of 18 000 ft at the end of the sixteenth week there was an increase in hemoglobin of 74 per cent and an increase in number of erythrocytes of 84 per cent During the period following the anoxia hemoglobin and red cell values decreased to original values In all instances, values below the original control levels were attained as though there had been an overshooting of the mark.

(1) J Aviation Med. 13 170 176 September 194

Hemoglobin values tended to reach control levels earlier than red cell values Average time in four dogs was eight weeks for hemoglobin and nine weeks for erythrocytes

It was concluded that discontinuous exposure to anoxia is capable of producing a noticeable degree of acclimatization the degree as measured by the amount of hemoglobin and erythrocytes being directly proportional to the severity of anoxia and the length of time of exposure If aviators actually show signs of acclimatization they should be better able to perform both physical and mental tasks at high altitudes A certain amount of acclimatization would increase their ceiling However regardless of the amount of acclimatization which a pilot may acquire it will be necessary to wear an oxygen mask above a certain critical level

Effects of Heightened Negative Pressure in the Chest Further Experiments on Anoxia in Increasing Flow of Lung Lymph Madeleine F Warren Delores K Peterson and Cecil K Drinker[2] (Harvard Univ) describe the anatomy of the lung lymph drainage in the dog and demonstrate that lung and heart lymph enter the blood through the right lymphatic duct They believe that cardiac activity measured through output remaining steady fluctuations in lymph flow from the right duct reflect changes in production and flow of lymph

In the first group of experiments the flow of lymph from lungs and heart was observed during breathing against abnormal inspiratory resistance The results showed that a large increase in negative intrathoracic pressure drew fluid from the lung capillaries into the lung parenchyma and under the excessive strain not only plasma but red cells left the lung capillaries to be returned to the circulation by the lung lymph When obstruction to inspiration was removed the red cell content of the lymph disappeared at once an interesting commentary on the rapidity with which nonameboid cells reach avenues of lymphatic drainage in the moving

(2) Am J Physiol gy 137 641 648 November 1942

breathing lung These results indicate the influence of extravascular negative pressure in producing transudation of fluid from the lung capillaries into the lung parenchyma

In a second group of experiments lung lymph was collected during anoxia produced by breathing gas mix

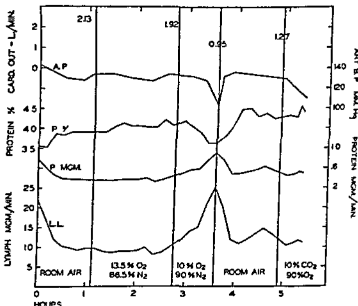


Fig 2 —Eff ct f l w ring alv lar oxyg n Dote w th figu es cardia o t put n l te p m ute upp c rv *A.P* rte l bl od p es u sec d curve *P %* pe cent prote n in lu g lymph third curv *P MGM* p otein n l g lymph in n ll g m p m n t Between vert l l num l b e thed gas mixtu e de ig ted ate and st k f re p at ry pump uniform throughout

tures containing low amounts of oxygen Figure 2 shows the results Artificial respiration with air was used first After the initial high lymph flow which invariably follows cannulation of lung or other lymphatics due to temporary obstruction during operative procedures, the lymph flow became very steady at about 9 7 mg per minute Blood pressure became constant and cardiac

output at the close of the period of ventilation with room air was 2.13 L per minute Ventilation was then shifted to a mixture of 13 5 per cent oxygen and 86 5 per cent nitrogen Lymph flow and blood pressure remained un changed and cardiac output was 1 92 L per minute After 1 hour and 35 minutes administration of this mix ture during which arterial oxygen saturation fell from 16 08 to 9 48 volumes per cent a second shift in ventila tion was made this time to 10 per cent oxygen and 90 per cent nitrogen Immediately the output of lung lymph rose however cardiac output fell to 0 95 L per minute and arterial oxygen saturation to 4 23 volumes per cent when it became necessary to return to ventilation with room air As soon as this was done lymph flow from the lungs fell to normal level and was undisturbed in the final period of the experiment when a mixture of 10 per cent carbon dioxide and 90 per cent oxygen was used

The changes in production and flow of lung lymph during anoxia cannot be attributed to increased cardiac output *or extension of the filtering bed of the lung* capillaries since cardiac output fell markedly during anoxia Consequently it must be concluded that when sufficient oxygen is not available the lung capillaries promptly become abnormally permeable but if this con dition is not allowed to go too far they readily return to normal by ventilation with adequate oxygen

The Genesis and Resolution of Pulmonary Transu dates and Exudates are discussed by Cecil K Drinker and Madeleine Field Warren[3] (Harvard Univ) Be cause of the vast extent of the pulmonary capillary bed and the great elasticity of the lung tissue it is probable that the pressure in the pulmonary capillaries is low—about 5 to 10 mm Hg instead of 20 mm for typical systemic capillaries The colloid osmotic pressure of the blood going through the lungs is however normal and much higher than the capillary blood pressure (Fig 3) To follow the production of pulmonary transudates a

(3) J A M A 1 2 69 273 M y 29 1943

simple experiment was carried out (Fig 4) Although the results seem obvious, they are particularly important today, when different types of masks are produced without much knowledge of what abnormal resistance to breathing may accomplish Severe respiratory movements which increase negative pressure in the chest will tend to produce pleural and pulmonary exudates even if oxygen lack is avoided Anoxia is another potent factor of pulmonary edema in that it alters the permeability of the pulmonary capillaries toward increased leakage The clinical implications of the experimental findings are obvious The capillaries of the lungs are in a unique position They gain their oxygen from the air, not secondarily from the blood Clinical experience has taught that when the physician decides that a patient needs oxygen, he is about 12 hours late If one waits until the leakage from the pulmonary vessels is pronounced it will be difficult to check the cycle that has begun

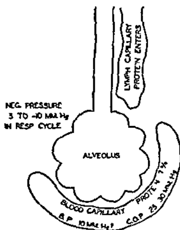
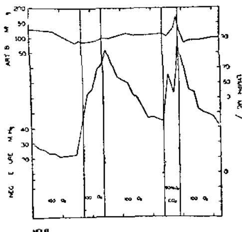


Fig 3 —Diagram of alveolus blood capillary and lymphatic in m mmalian tho x

If irritation by chemicals viruses or bacteria causes exudation from the pulmonary capillaries the results for the patient are usually worse than when transudation occurs Entrance of the air into the alveoli is blocked by coagulated exudate and cells in the finer bronchi and alveoli The pulmonary lymphatics in turn may readily be plugged by thrombi, and the situation makes for maximal difficulty in lung function Not only does exudate flood the lungs but fibrin formation interferes with removal of the exudate Solution of the exudate and

removal of small molecules through vascular absorption is the most efficient and rapid means of clearing the lungs of exudates If the irritant does not destroy cells extensively coagulation of the exudate may be slight



F 4—Lymph fl w s esult f b th g g t p t ry ist ce Uppe urv A P rt l p m ddl e R.D L lymph f m ght lymph t c du t n mill gr m p m t l w urv N.P negativ p u n h t Lymph fl w b m 11 mg a m ut ft 1½ h u of sist d b th ng Wh n sp t w mped d by tt n w l t lymph fl w t 8 5 mg m t On em l f t fl w f ll but cr sed wh t w mp d d 10 p t b n d d n dd d to xyg t f m x m l p t ry eff rt

and it will drain steadily through the lymphatics

Animal experiments and clinical observations have shown that after certain types of gassings there is a period of varying length in which the victim is quite normal This does not occur if the gas is too concentrated but in the case of the common offenders—nitrogen dioxide chlorine and phosgene—the individual may have breathed a fatal dose of the gas and not show dangerous symptoms for some time The experimental animal finally drowns in the pulmonary exudate which though it accumulates some hours after injury eventually clots owing to cell damage It is an interesting fact that

though the lung capillaries are caused to leak freely they do not fail to conduct blood What fails is oxygenation of the blood The only way to combat it is by early use of pure oxygen preferably under pressure, so as to overcome the abnormal barrier between the alveoli and the blood

Fat Metabolism in the Lungs was studied by P L MacLachlan[4] (West Virginia Univ) in male albino mice Results revealed that the lipemia which normally accompanied fat absorption from the intestine reached its maximum five hours following administration of a high fat diet and amounted to an increase of 43 per cent over the control level The lipid content of the lungs of mice maintained on a standard diet varies from 2 96 to 4 10 per cent average 3 46 per cent Variation is confined mainly to the neutral fat and cholesterol fractions Following administration of a high fat diet no significant increase over the control level was evident The phospholipid content of the lungs during this period was strikingly constant variation in total lipid was due chiefly to changes in the acetone soluble fraction Fasting mice will completely deplete their fat reserves in 48 hours and at the same time show a marked increase in liver fat During such a period of rapid mobilization and utilization of stored fat the lipids of the lungs fail to show significant changes from normal These observations do not support the conclusion that the lungs actively participate in fat metabolism

(4) J Bi l Chem 146 45 48 Nov mbe 194

DISEASES OF THE PLEURA AND MEDIASTINUM

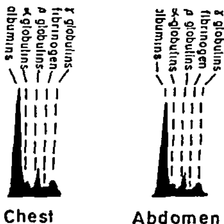
Association of Hydrothorax with Ovarian Fibroma (Meigs s Syndrome) The importance to the internist as to the gynecologist of keeping in mind the facts that a benign ovarian tumor may cause hydrothorax as well as ascites and that the simplest of laparotomies uniformly results in complete relief of the thoracic and abdominal features of the syndrome needs general recognition W W Herrick T Lloyd Tyson and B I Watson (New York City) report a case

Woman 75, stated that 1[1] year before fluid had been aspirated from the right thoracic cavity At present apart from emphysema and what was interpreted as pleural adhesions at the base of the right lung there were no signs of active dis ea e in the che t On fluor scopy the right half of the di phragm was judged to be adherent to the chest wall and moved little on inspiration Pulmonary fields were relatively clear Three months later there were coi iderable edema of both feet and clubbing of the fingers Sign of fluid at the base of the right lung were unequivocal The first thoracocentesis produced 1 000 cc straw colored fluid No polymorphonuclear leuko cytes or cells containing mitoses were seen During the subs quent 14 months nine aspirations were performed A deferred pelvic examination revealed a tumor in the right ide of the pelvis suggesting ovarian enlargement On operation a bilat eral ovarian tumor was removed which on examination proved to be fibroma The signs of remaining hydrothorax cleared in a week and there has been no recurrence The liver previously large and firm diminished in size and hardness returning to normal in 6 week

Fifteen cases of association of hydrothorax and ovar ian fibroma were collected from the literature by Meigs in 1939 The correlation of the two has not yet been satisfactorily explained Whether the permeability of the pleura is increased reflexively by production of tox ins that circulate with the blood by allergic effects or by hormonal influences is a matter of speculation

(5) A h I t Med 1 3 0 376 M h 1943

A Further Contribution to the Syndrome of Fibroma of the Ovary with Fluid in the Abdomen and Chest (Meigs s Syndrome) is presented by Joe V Meigs S H Armstrong and H H Hamilton[6] (Harvard Univ) Since 1937, when this syndrome was first presented 27 authentic cases have been reported and it has been discovered that Lawson Tait described a similar case in



Fi 5 —A ea of skewed probabil ty curve lying below each pe k is measur of elative co tratio s of protein c mpone t noted bo peak Beyond l ght difference in total a ea (ep esenting difference in total protein c n ent atio s at wh ch me urements were m de) patt ns are essent ally d ntical

1892 In some cases there has been a tremendous accumulation of fluid in the chest with only small amounts in the abdomen The fluid may accumulate overnight after the chest has been tapped there being as much in the chest as on the previous day The amount may necessitate many tappings Cachexia may appear the patient being unable to keep up the supply of fluid and dehydration and death may ensue yet the amount of fluid in the abdomen, its probable source may remain within limits easily compatible with life The reverse may be true but it is not so common

How the fluid finds its way into the chest is not

(6) Am J Obst & Gynec 46 19 37 J ly 1943

known In two cases reported here 2 cc India ink was injected into the abdomen Chest taps performed later showed the same concentration in the chest as in the abdomen The particulate carbon evidently passed from abdominal to chest fluid quickly and easily In the same two patients fluid in the abdomen and chest were identical with respect to protein components measured (Fig 5)

The authors emphasize that three important investigative problems emerge from observations on Meigs s syndrome (1) the mechanism whereby ovarian fibromas give rise to abdominal fluid (2) the mechanism of the hydrothorax (3) the question as to whether similar mechanisms operate in instances of combined hydrothorax and ascites where the primary disease is other than fibroma of the ovary

Cullen Kelly and others have shown that fluid may be present in the abdomen in lesions other than ovarian fibroma Whether this fluid is similar to that found in patients with fibroma has not been proved though it may be considered probable In most cases of uterine fibroid with fluid there are adhesions of omentum to the tumor or twists of the pedicle not present in fibromas

It remains for joint investigation by thoracic surgeons and others to demonstrate the presence of diaphragmatic perforations of small or large size and of the rarely reported pleuroperitoneal tubes and to determine the direction and degree of penetrability of the diaphragmatic lymphatics

The syndrome of ovarian fibroma with hydrothorax and ascites is of practical clinical significance It occurs sufficiently often that it must always be considered in a differential diagnosis of abdominal and chest fluid Patients thought to have cancer with metastases to the chest should have thorough consideration from the standpoint of this possibility Some patients have died without proper surgical relief and some who were doomed because of considered inoperable malignancy are now well

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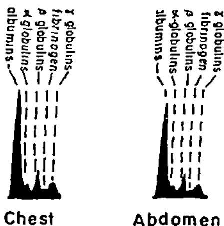


Fig 5 —Area of skewed probability curve lying below each peak is measure of relative concentrations of protein component noted above peak Beyond slight difference in total area (representing difference in total protein concentrations at which measurements were made) patterns are essentially identical

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Hemothorax in Blood Dyscrasia Paul Freedman Samuel Levine and Leon Solis Cohen[7] (Philadelphia) report two cases

CASE 1 —Man, 22, with hemophilia, complained of spontaneous, intense left chest pain for 36 hours and of passage of two tar colored stools He appeared exsanguinated, slightly cyanotic and restless Respiratory rate was 26, pulse 80, temperature 97 F and blood pressure 80/20 There were signs of fluid in the left chest X ray showed a homogeneous density extending from the left apex to base Two days after admission 450 cc fluid blood was obtained from the left pleural cavity Two more aspirations were done and he was given several transfusions He was discharged 30 days after admission greatly improved

CASE 2 —Man 26, had been hospitalized previously for marked thrombopenia On present admission he gave evidence of chronic exsanguination *Rales and dulness were present at* both pulmonic bases and the abdomen was distended There were marked hypochromic anemia and leukopenia and the platelet count was 5 250 Five days after admission there were *signs of fluid in the left chest and seven days later, evidence* of displacement of the mediastinum and respiratory embarrassment Thoracocentesis yielded 450 cc bloody fluid One more aspiration was performed He became septic, the abdomen was *distended and he had bloody stools Incision and drainage* of the left chest yielded pus He died two weeks later Autopsy revealed intestinal hemorrhage perforated diaphragm, left sanguinopurulent empyema and necrosis of the left lower lobe of the lung

It is suggested that aspiration in such cases is usually indicated after 48 hours for blood left in the pleural cavity may form fibrin clots requiring thoracotomy The entire collection should be removed in one or two aspirations as the fewer the punctures the less danger of infection Replacement pneumothorax is of questionable value in controlling bleeding and increases the tendency to adhesions and its serious consequences

[As stated artificial pneumothorax is not indicated to control bleeding in such cases however its use in other types of hemothorax caused by bleeding from a tear of an adhesion or of the visceral pleura is often effective in stopping the hemorrhage With aseptic technic the pleura seldom becomes infected —Ed]

Traumatic Hemothorax is discussed by A Tudor Ed

(7) Am J M S 0 69 696 May 1943

wards[8] on the basis of 204 cases of chest wounds and crush injuries The causes of death in such injuries are hemorrhage and infection The most important problem is prevention of sepsis The percentage of septic infection of the resulting hemothorax was 21 9 per cent with penetrating or perforating wounds and 11 3 per cent with nonpenetrating wounds The latter figure indicates that infection may spread from the lung or blood stream in crush injuries With penetration of the pleura by foreign bodies the amount of infection carried in by the object varies according to its size shape and surrounding conditions Large and irregular foreign bodies cause much laceration and tend to carry in portions of clothing while smaller and smoother objects are less likely to do so Retention of effused blood in the pleura has a definite bearing on incidence of sepsis for the fluid provides the ideal culture medium for growth of bacteria Most injuries due to missiles and crush injuries have associated hemorrhage into the pulmonary tissue In most cases absorption of the hematoma is rapid and continuous but occasionally it becomes infected At this stage the roentgenogram shows a translucent central area with fluid level Most of these clear by postural drainage which should be given a trial before operation is undertaken Early removal of small retained missiles is unwarranted for the difference in incidence of infection between cases with retained small missiles and those in which the missile passed through the chest is small

Sulfathiazole should be given as soon as possible after injury The hemothorax should be aspirated and replaced by a much smaller quantity of air at the end of 24 hours but certainly before 48 hours Simple aspiration without air replacement (replacement at subsequent aspirations may cause maintenance of a large pleural pocket) should be continued at regular intervals until the pleura remains dry When hemoglobin and blood count show a substantial fall blood transfusion should

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be given Should infection supervene during the period of aspirations it is immediately recognized and the dose of sulfathiazole should be increased The infecting organisms should be identified, and in absence of anaerobes aspiration should be continued until formation of definite pus when drainage should be established by rib resection When anaerobes are present repeated aspirations may permit escape of infected fluid along the needle track into the chest wall causing virulent cellulitis This can be prevented by making a 3 in vertical incision in the chest wall over the area of aspiration deepening the incision to the ribs and intercostal muscles and packing firmly with gauze soaked in flavine emulsion A barrier of granulation tissue is formed as a result and subsequent aspiration is carried out through the shut off area Respiratory exercises to restore full pulmonary function should be begun within 48 hours of drainage if the patient s condition permits Drainage must be continued until the cavity is obliterated by approximation of the pleural layers

Tension Pneumothorax and Mediastinal Emphysema after Tracheotomy Analysis of 17 cases of pneumothorax in 126 tracheotomies performed at Willard Parker Hospital New York City in the past decade is presented by A Harry Neffson[9] (M C A U S) The 17 cases represent an incidence of 13 5 per cent With an increase in relative frequency of tracheotomy from 4 3 per cent in the first five years to 19 4 per cent in the last three years there was a lowering of incidence of pneumothorax from 25 to 8 per cent Of the 17 patients 12 were males and 5 females aged 6 months to 4 years the greatest incidence occurring between 1 and 2 years In 8 cases the pneumothorax was unilateral and mortality rate was 25 per cent in 9 it was bilateral and mortality rate was 89 per cent Pneumothorax occurred in 18 per cent of cases in which intubation did not precede tracheotomy and in 12 per cent of cases with intu

(9) Arch Otolaryng 37 339 January 1943

bation Pneumothorax was noted a few hours after operation in nine cases one to three days after operation in five during operation in two and post mortem in one Mortality in 10 cases in which tracheotomy was performed on admission or within 24 hours was 80 per cent and in 7 in which it was performed 2–21 days after admission it was 28 per cent There were 30 cases of mediastinal emphysema in 5 of which mediastinitis and empyema were contributing causes of death Subcutaneous emphysema was frequent but presented no problem

Since the most frequent cause of pneumothorax and mediastinal emphysema following tracheotomy appears to be the sucking in of air through the tracheotomy wound into the mediastinum this should be prevented by eliminating respiratory obstruction during operation eliminating postoperative respiratory obstruction and avoiding opening of avenues for the tracking down of air into the mediastinum Early diagnosis of pneumothorax is essential to prevent needless deaths Diagnosis is based on roentgen evidence appearance of dyspnea diminished excursion of the affected side and diminished breath and voice sounds with hyperresonance or tympany During tracheotomy presence of a pleural bubble in the wound enlarged with each expiration is good tentative evidence of presence of pneumothorax on mediastinal emphysema Mediastinal emphysema can be recognized by crepitation heard with each heart beat when the stethoscope is firmly pressed to the cardiac area With severe emphysema there are cyanosis dyspnea rapid pulse congestion of the superficial veins of the neck low blood pressure substernal discomfort and pain

A unilateral or even bilateral pneumothorax causing no embarrassment requires no immediate action the air is usually absorbed in a few days In tension pneumothorax immediate and continuous or repeated decompression is necessary one of the best methods being closed underwater drainage If this procedure presents

difficulties a finger cot with the tip cut off can be attached to the hub of the needle which will act as a one way flapper valve allowing the air to get out but not to get in A third method is use of pneumothorax apparatus to remove enough air to bring pressure down to normal

Chronic Empyema is discussed on the basis of a study of 346 cases by O Theron Clagett and V Duncan Shepard[1] (Mayo Clinic) The relative frequency of this condition is decreasing (Fig 6) Many of the cases that occurred in 1923 1924 and 1925 were the results of the influenza pandemic of World War I Chronic empyema occurs largely in early adulthood It is not a disease but a complication and in this series it accompanied or followed pneumonia influenza pleurisy tuberculosis trauma and the acute exanthemas in this order The most common causes of chronicity are inadequate drainage,

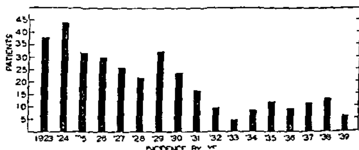


Fig 6—D cr a e n lat e freque cy of hroni empyema M y in t aces in 19"3 19 4 and 19 5 were r ults of infl en a pandem of Wo ld Wa I.

tuberculosis too late drainage (too late because the empyema was not recognized) bronchial fistula and bronchiectasis (Fig 7)

The commonest complaints of the patients on admission were sinus in the thorax cough expectoration daily fever and pain in the thorax Physical observations most often made were sinus in the thorax impaired resonance of the thorax immobility of the chest and clubbed fingers One half of the 115 patients whose cavities were

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measured presented a cavity with a capacity of less than 500 cc about one fourth had cavities of 500 to 999 cc and another fourth had cavities of 1 000 cc or more There was no demonstrable correlation between the clin

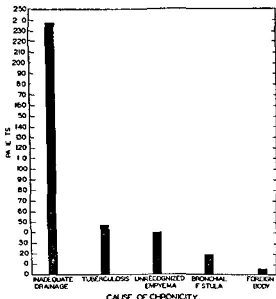


Fig —Inadeq t d ag w p hl f p lt m ng 38
p t t f gn b dy g n f quent f h ty n m y t t
b k w fifth f q n th

ical type of antecedent illness and the type of bacteria cultured from the empyema cavity

Roentgenograms of the thorax were made for 334 patients 314 disclosed some type of pleural reaction (usually thickening or fluid) in only 20 was no reaction visible and in only 6 were the results normal In such an advanced state of empyema as that in which these patients presented themselves diagnosis was not difficult

Prophylaxis of chronic empyema is establishment of early adequate drainage in every instance of acute

empyema Clagett and Shepard found that the more radical the original treatment the shorter the patient's stay in the hospital and the lower the mortality This speaks for open drainage as early as it can be done safely Many bronchial fistulas will heal spontaneously or with only minor surgical attention Presence of bronchial fistula does not increase the mortality or morbidity rate of chronic empyema Closed drainage alone resulted in cure for only 8 per cent of this group of patients However closed drainage is valuable in that it keeps the cavity drained until the mediastinum has become fixed enough to allow open drainage to be instituted safely Open drainage of some kind was required in 71 per cent of the cases Thoracoplasty was used in only 5 per cent This shocking and mutilating operation should be reserved for patients not responding to less formidable procedures

Deaths in the hospital after operation (5 per cent) were due to operative shock and spread of infection by contiguity or metastasis (the commonest form of the latter was abscess of the brain, seen in three cases) Nonfatal complications were thoracic sinus, exacerbation of coexistent nephritis metastatic infections and tuberculosis of the spinal column

In answer to written inquiries 164 patients stated that their general health was excellent and that they had been able to resume their usual mode of living this period of good health was of varying duration (1 to years) depending on how long previously surgical treatment had been carried out

Metastatic Brain Abscess Complicating Inconspicuous Pulmonary Suppuration in the Presence of Chronic Nontuberculous Empyema is discussed with a report of six cases by Robert W Buxton and M L White Jr [2] (Univ of Michigan) These six cases were encountered in a series of 343 cases of empyema observed from 1934 to 1941 an incidence of 4 5 per cent

(2) Surgery 13 309 315 February 1943

Adequate and dependent drainage of the empyema was established in four of the six patients after hospitaliza tion No definite correlation was noted between manipu lation at the empyema drainage site and onset of cerebral symptoms In four cases the cerebral abscess was soli tary in one multiple and in one multilocular Encap sulation of the abscess was absent in all instances All six patients had purulent meningitis and in two rup ture of the abscess into the adjacent lateral ventricle occurred Exploratory craniotomy was performed in three cases In two the abscess was drained surgically and in one it was evacuated through the exploring needle Appropriate chemotherapy with one of the sulfonamides was carried out in these three cases

All six patients died Duration of symptoms from on set to death ranged from 5 to 23 days Necropsies showed that in four the previous empyema space was obliter ated In five there were varying degrees of chronic parenchymal pulmonary suppuration considered a more probable source of emboli than the pleural infection In the case in which this was absent empyema was consid ered the most likely source of emboli to the brain

Of 72 cases collected from the literature 82 per cent arose from intrinsic pulmonary suppuration and only 18 per cent or 13 cases were attributed to empyema The authors believe that a high proportion of these 13 cases would have shown some suppuration in adjacent pulmonary tissues if these had been closely examined and that if such pulmonary suppuration were present it was a more likely source of metastatic brain abscess than the empyema

Esophagopleural Fistulas W Cohen (Portland Ore) and E A Sindell[3] (Bethlehem Pa) report a case and review the literature

Woman 30 with tuberculosis of the left lung was treated with pneumothorax for one year The sputum became nega tive and refills were stopped Six months later empyema de veloped which was not controlled by oleothorax or aspiration

(3) W t J S g 50 238 249 M y 1942

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ticulum of the esophagus In one case there were necrotic mediastinal lymph nodes The tuberculous esophageal ulcers in the present case are thought to have been secondary to a spilling of the tuberculous pleural fluid into the esophagus through the fistula The prognosis in chronic empyema is poor while that in nontuberculous empyema is comparatively good Of the 17 patients 10 died 5 were cured 1 was living at the time of the report and the outcome of 1 is not known Treatment consists of preventing oral contamination of the pleural space adequate drainage of the pleural space and obliteration of the empyema space

Congenital Cysts of the Mediastinum are described by Herbert A Carlson[4] (Minot N D) Epidermoid and dermoid cysts and teratomas have one feature in common namely they contain tissue derived from ectoderm and therefore have been grouped under one term—teratoma They usually occur in the anterior mediastinum but may protrude laterally and posteriorly to occupy a major portion of either thoracic cavity or extend from the superior mediastinum to the base of the neck Some teratomas are malignant Teratomas are believed to develop from cells which have become segregated early in life They often produce no symptoms for 20 to 40 years Pain cough and dyspnea and occasionally expectoration of blood hair and other cyst material constitute the symptoms X rays show a rounded nonpulsating mass in the anterior or superior mediastinum or extending into the lung field Cystic lymphangioma is less common than teratoma and is characterized by formation of multiple cysts Pericardial coelomic cysts are simple thin walled asymptomatic growths Two cases have been reported by Lambert

Ciliated columnar respiratory epithelial cysts or bronchiogenic cysts may contain all of the tissues found normally in the bronchial wall They are cysts of the posterior mediastinum or the posterior portion of the

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and irrigation One year after development of the fluid which had previously shown only tubercle bacilli, a variegated bacterial flora was recovered from the pleural exudate Yeast cells were also found An esophageal fistula was demonstrated by barium meal Thoracotomy was performed and feedings were given via stomach tube Signs of intraperitoneal hemorrhage soon developed with bloody drainage from the thoracotomy tube The patient died one month after formation of the esophagopleural fistula Postmortem examination disclosed an esophageal fistula at the level of the fourth dorsal vertebra, a healing cavity of the left upper lobe, disseminated miliary tuberculosis a chronic left tuberculous empyema multiple recent tuberculous ulcers of the esophagus in the region of the fistula and perforation of the left leaf of the diaphragm with intraperitoneal bleeding from a rupture of the spleen

Sixteen additional cases are reviewed from the literature Of the 17 patients 12 were males 3 were females and the sex of 2 was not mentioned Ages ranged from 16 months to 59 years The average age was much lower in the nontuberculous than in the tuberculous group The fistula communicated with the left pleural space in nine cases and with the right in seven but the communication was not mentioned in the other case The level of the fistula in 14 of the 15 cases in which it was mentioned was in the region of the bifurcation of the trachea in the other case it was 3 in above the diaphragm The empyema was tuberculous in seven cases nontuberculous in six and not mentioned in four One or more of the following symptoms occurred dysphagia vomiting of pus increase in toxicity change in physical signs from those of hydrothorax to those of hydropneumothorax foul fatty expectoration fetid odor of the breath food particles in the pleural exudate or drainage foul sour odor of butyric acid or fermentation to the pleural exudate tasting or vomiting of the irrigating fluid and sudden increase in the amount of pleural drainage In three of the case reports empyema necessitatis was mentioned In 12 cases the esophageal fistula developed after surgical drainage of the pleural space Two of the fistulas were associated with a traction diver

DISEASES OF THE BRONCHI INCLUDING ASTHMA

Chronic Bronchitis in the Aged is discussed by Trevor H Howell[5] (Royal Hosp Chelsea) The climatic predisposing factors in aged subjects are cold fog and dampness During winter the cough of an elderly bronchitic becomes worse if not taken care of he may develop bronchial spasm pyrexia or both In such cases the ultimate prognosis is bad for after one or two such attacks congestive heart failure supervenes In an elderly bronchitic with suspected pneumonia pyrexia and not consolidation should be taken as indication for chemotherapy to prevent cardiac involvement Elderly patients with bronchial spasm are best controlled by adrenalin 0 5 1 cc hypodermically Usually the effect lasts 8 or 12 hours after which the injection may be repeated Some practitioners object to adrenalin on the grounds that it raises the blood pressure but this has not occurred in Howell s experience with elderly patients In fact the blood pressure in persons with chronic bronchitis is low for their age and tends to fall during the infection uninfluenced by adrenalin

Care of the elderly bronchitic should be directed toward preventing the lung bases from becoming plugged with sputum and functionally impaired If a patient huddles in bed so that the lower part of his chest cannot expand properly it is best to nurse him sitting upright in a tall armchair often with surprising results The medication at the Royal Hospital consists of a mixture of 10 gr tincture of ipecac 2 gr ammonium chloride and 5 gr ammonium carbonate to the dose This seems to diminish the sputum rather than to increase it thus supporting Alstead s claims The most effective method of bringing up the sputum is to give 1/ pt hot water before breakfast which seems to clear the bronchial

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superior mediastinum and are usually found in the neighborhood of the bifurcation of the trachea They are believed to originate from the foregut, from the respiratory buds or their derivatives Large bronchial cysts may produce symptoms early in life by obstructing the air passages Dyspnea may be continuous or come in attacks and the infant may present dysphagia and croupy or brassy cough Diagnosis may be difficult when the cyst is small and surrounded by atelectatic or consolidated lung tissue Bronchoscopy should then be done

Gastric, or gastrogenic cysts reproduce the structure of the stomach and enteric cysts are similar to gastric cysts except that they are lined with intestinal mucosa Both occur in the posterior mediastinum and are said to have derived from the omphalomesenteric duct Since the cysts attain considerable size early physical signs such as dulness or flatness and decrease of breath sounds usually on one side posteriorly may suggest presence of fluid in addition to dyspnea cyanosis cough and dysphagia Aspiration of fluid containing hydrochloric acid is pathognomonic for gastric cyst

In surgery of a mediastinal cyst the one stage operation is ideal but preliminary drainage has given sufficiently good results to justify its use especially in infants *with dyspnea cyanosis or dysphagia*

Carlson reports one case each of teratoma bronchial cyst and gastric cyst

[These cysts may be discovered accidentally by x ray examination of the chest If there are no related symptoms one usually hesitates to recommend operation The prospect of slow growth and insidious damage should always be considered in weighing the situation. In most cases the cyst should be removed by an experienced thoracic surgeon —Ed]

pulmonary artery is not the same as pulmonary atelectasis but is fibrotic organization of hemorrhagic necroses However the roentgen signs of fibrotic shrinkage of the lung and atelectasis are the same

With regard to formation of bronchiectasis it is concluded that the mechanical forces (high negative intrapleural pressure) operative when following bronchial occlusion the alveolar air is absorbed do not tend to dilate but to constrict the bronchi Uncomplicated pulmonary atelectasis per se cannot therefore be a cause of bronchiectasis Even when the access of air to the bronchial tree was not prevented (by ligation or obstruction from within) namely in ligation of the pulmonary artery the increased negative intrapleural pressure did not produce dilatation of the bronchi unless the process was complicated by accidental or intentional infection Following partial obstruction of the bronchus of a lung patchy atelectasis overinflation and emphysema of the lung occurred but no bronchiectasis

On the other hand within three to four weeks infection may produce most extensive saccular bronchiectases in a formerly atelectatic lung Furthermore the increased negative intrapleural pressure at the side of an atelectatic lung is an irrelevant factor in the pathogenesis of bronchiectasis since bronchiectases of the same intensity developed within the same time whether or not highly negative intrapleural pressures were prevented by induction and maintenance of pneumothorax The arrangement of the collapsed alveolar tissue which is stretched in the direction parallel to the circumference of the dilated bronchi among other factors suggested strongly that the pressure of the inflammatory exudate within the bronchi which cannot be evacuated because of bronchial obstruction is probably an important factor in dilating bronchi whose walls have become weakened by inflammatory involvement The infection most likely to produce bronchiectasis is one which is virulent enough to cause a purulent inflammation within the

tubes for the day the same amount can be given at night

[When spasm of the bronchi is a complicating factor inhalation of a nebulized bronchodilator such as neosynephrin or vaponefrin may be helpful —Ed]

Atelectasis and Bronchiectasis An experimental study of the relationship of the two conditions was carried out in rabbits by Joseph Tannenberg and Max Pinner[6] (Montefiore Hosp New York City) First evidence of developing atelectasis was found in the shift of the heart to the side of the obstructed lung within 50 to 60 minutes after bronchial obstruction when the other roentgen signs of atelectasis particularly increased density were not yet recognizable The experiments showed that complete atelectasis may exist for a long time up to several months without complicating processes within the lung provided the atelectatic lung does not become infected Obstructing foreign bodies can remain for many weeks in bronchi without producing any disturbances save a strictly local dilatation of the bronchial tube at the site of their lodgment The most probable explanation for this unexpected observation is that the dilatation of the bronchus at the bed of the foreign body soon permits *the air to pass through the obstruction* Pulmonary atelectasis up to 10 days duration produced by bronchial obstruction from within may completely disappear after removal of the obstructing foreign body In pulmonary atelectasis produced by bronchial obstruction from within or from without the bronchi of all sizes distal to the obstruction participate in the pulmonary collapse becoming *as much constricted as is permitted by* the structure of their walls the reason for their collapse is apparently the same as that for the parenchymal collapse The experiments also showed that the potential space made available by shrinkage of the atelectatic lung is filled All neighboring structures and organs which are directly or indirectly under atmospheric pressure tend *to occupy the space formerly filled by the expanded* lung Shrinkage of the lung following ligation of the

(6) J Thora c Surg 11 571 616 August 194

of death whereas of those who did not have bronchiecta sis pneumonia was the primary or secondary cause of death in only 18 per cent Because 41 of the 47 patients with bronchiectasis were 40 or more a comparison was made between them and 961 patients of a consecutively recorded series of the same age range In this older age group 85 4 per cent of the 41 patients who had bronchiectasis also had pneumonia whereas among the 961 patients without bronchiectasis incidence of pneumonia was only 40 6 per cent To determine the part which surgical operations might have played in this study each group of patients who had pneumonia was divided according to whether or not the pneumonia was post operative It was found that 282 patients or 56 3 per cent of those who did not have bronchiectasis had pneumonia which was postoperative whereas 17 patients or 44 7 per cent of those who had bronchiectasis had pneumonia which was postoperative This would indicate that the frequent occurrence of pneumonia among the patients with bronchiectasis was not due to postoperative complications

[R current pneumonia is the most serious sequel of bronchiectasis Frequently the acute infection n tiates chronic suppuration —Ed]

Bronchiectasis without Disability L C Martin and F R Berridge[8] (Cambridge Univ) report on 25 cases of bronchiectasis seen in two years among soldiers 21 were 19 29 the others older Cough and sputum were presenting symptoms in 23 dry pleurisy in 1 and evening pyrexia in 1 Subsidiary symptoms were dyspnea and wheezing on exertion with recent lassitude and malaise in a few cases There was a history of hemoptyses in seven Except for the patient with dry pleurisy none of the men were incapacitated and nearly all were graded A1 in the army those who were not had been down graded for other than chest conditions The cough was intermittent in 23 cases and as a rule came on in winter after a sore throat cold or chill Sputum was produced

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bronchi but not virulent enough to produce the same kind of exudate within the alveoli but only a desquamative pneumonia More virulent infections apparently led to death before bronchiectatic changes could develop Bronchial and pulmonary infections never resulted in bronchiectasis when the bronchial lumens were not severely obstructed Intrabronchial aspiration of bronchiectatic exudate into the contralateral lung caused bronchopneumonia and not bronchiectases It must therefore be concluded that association of two pathogenic factors is necessary for the development of bronchiectasis infection and impairment of bronchial drainage

A comparison of the experimental observations with the changes seen in man makes it more probable that uncomplicated atelectasis per se has no bearing on the development of bronchiectasis There is however another relationship of these two conditions, both may be produced by the same cause Atelectasis in children and the other primary diseases which are found frequently in the histories of bronchiectasis patients are caused almost without exception by inflammatory conditions of the lung Bronchial exudate and inflammatory swelling *of the bronchial mucosa may close the bronchial lumen* and cause atelectasis in a short time

Bronchiectasis and Its Relationship to Pneumonia D C Campbell and H J Moersch[7] studied 47 cases in which diagnosis of bronchiectasis had been made on autopsy These cases were found in a consecutive series *of 1 191 autopsies an incidence of 3 9 per cent Of the* 47 patients 80 9 per cent had pneumonia of varying severity as compared with an incidence of pneumonia of 43 8 per cent among the 1,144 patients who did not have bronchiectasis The comparison is even more striking when it is limited to patients whose pneumonia was *a primary or contributory cause of death Thus 59 6 per* cent of the 47 patients with bronchiectasis had pneumonia which was either a primary or contributory cause

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Surgical Considerations of Bronchiectasis are discussed by Alton Ochsner and Michael DeBakey[9] (Tulane Univ) It is the consensus of experienced observers that of the chronic pulmonary affections bronchiectasis ranks second in frequency to pulmonary tuberculosis and may possibly surpass it From reports in the literature it has become increasingly evident that untreated and medically treated bronchiectasis is attended with a high mortality relatively short life expectancy and devastating morbidity Accordingly the significance of surgical therapy becomes apparent for it is the only means by which these consequences can be eliminated effectively and permanently With introduction of the single stage lobectomy by Brunn the high mortality associated with early attempts at operative removal of diseased lung steadily decreased Further refinements in preoperative care anesthesia and operative technic have reduced mortality to less than 3 per cent

Indications for operation in bronchiectasis depend on the patient s age and general condition extent of involvement and character and degrees of manifestations By instillation of lipiodol into the individual lobes under bronchoscopic visualization followed by postero anterior lateral and oblique roentgen projections (Fig 8) the extent and distribution of the process can be determined accurately in each lobe permitting precise assessment of the extent of operation necessary to produce cure Obviously unilateral involvement limited to one lobe or to the lower and middle lobes on the right and the lower lobe and lingula on the left offers much better surgical risk than bilateral involvement The latter however is not a contraindication to operation Age is an important factor Operative statistics have shown conclusively that lowest death rate is obtained in children and that it increases proportionately with age Operation is rarely indicated in persons over 45 Most patients do not survive that long unless the process is relatively

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by these patients either constantly or intermittently it was usually thick and yellow and never copious Specimens obtained from 18 of them were negative for tubercle bacilli There was a history of pneumonia in 13 cases in 10 of them during infancy or childhood There was a history of pleurisy in 8 cases and of bronchitis in 17 Only four had no history of any significant chest disease

Although some patients had bilateral bronchiectasis or considerable unilateral saccular disease none presented a toxemic or ill nourished appearance In five there was early clubbing of the fingers with shiny curved nails with some loss of the crevice between finger and nail bed only one example of gross or drumstick clubbing was seen Of the physical signs in the chest impaired note poor air entry and persistent rales were most common Physical signs alone often failed to distinguish between true bronchiectasis and chronic purulent bronchitis Straight roentgenograms permitted diagnosis of bronchiectasis in some cases and suggested it in others Bronchography however was essential for demonstrating the exact extent of the disease even when recognized in the straight film and for proving presence *or absence of bronchiectasis in doubtful cases* The oral technic for bronchography was used

Roentgen study of the sinuses in 17 revealed evidence of infection in 7

It is concluded that because of the apparently healthy appearance and little physical incapacity such patients are rarely seen in general hospitals in peacetime Expectation of life is less gloomy than has been generally assumed for patients with bronchiectasis

[In a chronic disease of this sort the criteria considered by the authors can hardly be accepted for long range prognosis Other experience indicates that most of these patients will get into serious trouble in their forties and fifties if not before depending on the extent and character of the bronchiectasis On the other hand the following article by Ochsner and DeBakey is a little too pessimistic at least for cases of limited cylindric bronchiectasis — Ed]

to consciousness following completion of the operation

The incision should be performed with a view to permitting adequate exposure ready adaptability to variations in the pathologic condition minimal trauma and ease of closure Accordingly the authors use for lower lobectomy a posterolateral approach with the incision beginning paravertebrally and extending forward along the seventh interspace to the anterior axillary line Of the two methods of lobectomy used—mass ligation with a tourniquet or individual isolation and ligation of the intrahilar structures—the latter is preferred because it permits application of better surgical principles and complete removal of diseased tissue Its technical performance however necessitates a thorough concept of the anatomic patterns and variations of the segmental divisions of the pulmonary vessels and bronchi

Drainage of the pleural cavity is provided by an intercostal catheter Negative pressure is applied to the catheter which is allowed to remain two to four days after operation in cases with minimal contamination and longer in tourniquet lobectomy cases Local application of a sulfonamide and its pre and postoperative administration have been recommended Meticulous postoperative care is essential especially during the first few hours and days

Surgical Treatment of Bilateral Bronchiectasis is discussed by Brian Blades and Evarts A Graham[1] (Washington Univ) At least 30 per cent of patients with bronchiectasis show bilateral involvement A sufficient number of successful bilateral lobectomies however has been reported to prove that bilateral extirpation of lung tissue can be accomplished The principal considerations are age and general condition of the patient amount of tissue involved and degree of involvement and severity of symptoms The authors believe that in older patients with bilateral bronchiectasis postural drainage supplemented by bronchoscopic aspiration should be given a

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mild and therefore does not require extensive surgery, those who do, have such extensive distribution that operative cure is precluded

In preoperative preparation every attempt should be made to eliminate sinus and focal infections and clear the bronchi of retained and infected secretions The latter is accomplished preferably by postural drainage and repeated bronchoscopic aspiration Bronchoscopic aspir



F 8 (left) —L teral film how b on h t t c nvolem nt of lingul part of l ft upper lobe as w ll as l ft low lobe

F 9 (ht) —S me p t ent as p eced ng e e l mo th afte em val of b on h ctat l ft low lobe

ation is also performed routinely immediately before and after operation Other preparatory measures include administration of sulfonamides and neoarsphenamine and a high calorie diet with vitamin supplements particularly vitamins B and C Regarding anesthesia the important desiderata are complete control of intrapulmonic pressure adequate facilities for aspiration of secretions in the respiratory passages during the operation maintenance of quiet respirations and high oxygenation, avoidance of distressing cough reflex and rapid return

Relation of Ciliary Insufficiency to Death from Asthma and Other Respiratory Diseases was studied by A C Hilding (Univ of Minnesota) on the basis of records and pathologic material from fatal cases of asthma influenza and bronchopneumonia

In one group of cases of asthma a striking and characteristic change in the bronchial epithelium was found consisting of substitution of goblet or goblet like cells for the normal columnar ciliated cells Apparently it is a true metamorphosis It seems to begin deeply within



Fig 10—Low p w ph t i g ph f b ch l p tl l n f t l f th f y du t M t ll l t i t t i f l i d ll rm ll f u d th p th l m f l t d ll d p f ld f ll d t t t f b h l

the individual cells with formation of a droplet of mucin which enlarges until it eventually lifts the plate of cilia from the end of the cell and escapes and the cilia become lost entirely (Figs 10 and 11) The secreted mucin however does not always escape completely It protrudes from the cell which produced it fusing with the mucinous mass in the lumen but still remaining attached to the interior of the cell (Fig 12) As the metamorphosis takes place the ciliary mechanism is lost and the characteristic viscid mucinous secretion accumu

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trial before surgical treatment is undertaken but that in young subjects radical treatment is the method of choice Children tolerate intrathoracic operations particularly well and it is desirable to eradicate the disease before irreparable physical and psychologic damage is done

Experience with 16 cases of bilateral bronchiectasis suggests that in young subjects surgical treatment can be successful if the two upper lobes are free from disease (the lingula of the left upper lobe is considered as the left middle lobe) Practically all patients with bilateral bronchiectasis will be benefited by extirpation of the bronchiectatic tissue on the most extensively diseased side When the contralateral disease is not far advanced unilateral lobectomy may at least temporarily relieve production of purulent sputum In three young subjects all of the pulmonary tissue except the two upper lobes (lingula of the left upper lobe was also extirpated) has been removed successfully Twenty lobectomies were performed in this series of 16 cases Four patients died—two of suffocation during operation due to flooding of the trachea one of pulmonary tuberculosis and one of staphylococcic septicemia

The chief danger from bilateral lobectomy is suffocation during operation or from early opening of the bronchus The upright position for lobectomy is suggested to minimize the danger of suffocation while the operation is in progress to relieve the necessity of rapid operating and to allow time for adequate closure of the bronchus to prevent postoperative empyema An upright position is also recommended during the postoperative period thus keeping the pleural cavity on the side operated on completely free from fluid by catheter drainage with suction The other important postoperative measures include bronchoscopic aspiration before the patient reacts from the anesthetic and temporary immobilization of the thoracic cage during the act of coughing as soon as the patient is awake

removed by the ciliary action had not this mechanism which normally removes them easily been destroyed

The pathologic material from the lungs of 12 patients who died of acute respiratory distress during the pandemic of influenza in 1918 was reviewed The bronchiolar epithelium in these cases had been entirely destroyed and all cilia with it

In all these groups Hilding believes the mechanical removal of secretion as a substitute for ciliary action is indicated with aspiration through a bronchoscope or a tracheotomy opening



F 1 —Ep th l l ll n ght nt h be m mu p d g c ll ted mu u t d h f d w th m n lum but m tt h d deep w th n ll wh ch p odu d t m l pp t h be n d gg d t f p t n b t t m l t d ll m n b th e d f m u t d

The study of the cases of bronchopneumonia is not completed

Treatment of the Acute Attack of Asthma is outlined by Joseph Weiner[3] (Yale Univ) For mild attacks in children syrup of ipecac 1 or 2 teaspoonfuls may be effective in dislodging a mucous plug and relieving the attack Ipecac should be used cautiously if dehydration is present A vaporizing spray of 1 100 solution of epinephrine is safe in children over 7 Ephedrine 1/4 1/4

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lates in the air passages The amount of secretion is *enhanced because the erstwhile ciliated cells as well as* the glands are secreting The difficulty of removal of the secretions is aggravated because a great deal of the mucin remains attached within the cell which produced it thus anchoring the mass to the wall When the air passages *become sufficiently filled the patient dies of* asphyxia

In a second group of cases of asthma the cilia were also lost, but the picture was essentially different Here chronic bronchitis with purulent secretion was prom



F g 11 —H gh m n ficat on of s m fi ld F gu 10

inent There was destruction at the surface of the bron chial epithelium and the ciliated cells sloughed away extensively In these cases too the air passages filled with secretion to such an extent that the patients died Presumably the stasis and accumulation occurred largely *because of loss of ciliary action*

One patient with tracheobronchitis also died in ex treme respiratory distress The ciliated epithelium was practically entirely destroyed and according to th necropsy notes all the bronchi contained viscid plugs of secretion Presumably these secretions could have been

removed by the ciliary action had not this mechanism which normally removes them easily been destroyed

The pathologic material from the lungs of 12 patients who died of acute respiratory distress during the pandemic of influenza in 1918 was reviewed The bronchiolar epithelium in these cases had been entirely destroyed and all cilia with it

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Fig 1 —Ep thel l ll in ght t h be me mu n p d c ll S cr ted m t d h f s d w th m m lum b t m n tts h d deep w th n e ll wh ch p du d t m u l pp t h be d gged t f po t n b t ct n m d ted ll m n n b th d of mu u tr d

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gr may be given orally for four to five doses at ¾ hour intervals If no relief is obtained it should be stopped Children given ephedrine over long periods become pale and irritable and may develop anorexia and bladder symptoms In case of intolerance to ephedrine ephetonine ½-¾ gr or propadrine hydrochloride ⅜-¾ gr may be used Ephedrine is more effective in combination with aspirin and phenobarbital

Cough in early stages is controlled by codeine with ammonium chloride for profuse expectoration terpene hydrate is added In dry and spasmodic cough a pertussis mixture of codeine sodium bromide and antipyrine should be used Small doses of potassium iodide 2-5 gr three times a day are effective in the spasmodic stage Adrenalin is the most effective drug in the acute attack care should be taken so as not to develop "adrenalin fastness" From 3 to 5 minims of a 1:1000 solution is given subcutaneously every ½ hour until relief obtains As an emergency measure it may be given intravenously by diluting 0.1-0.2 cc adrenalin in distilled water or the patient's own blood and injecting it slowly *When the attack continues uninterruptedly for 36 hours* despite treatment the patient is in status asthmaticus

Morphine should never be given in status asthmaticus It slows and deepens respiration and may cause cyanosis or even drowning in one's own fluid It should only be given in cardiac dyspnea with impending heart failure Atropine dries the mucous membranes and locks up the secretion thereby prolonging the attack The important measures to use in status asthmaticus are (1) hospitalization which breaks up the antigenic contact *and may be the only measure necessary in children* (2) administration of intravenous glucose in 5 per cent solution in distilled water (salt aggravates asthma) to combat dehydration and break up adrenalin fastness (3) administration of aminophylline intravenously 3¾ gr in a 10 cc ampule in children and 7½ gr in 20 cc diluent in adults These measures usually break up the

status asthmaticus after which small doses of adrenalin can be given subcutaneously Oxygen may be necessary in cyanosis If the attack continues despite all medication rectal anesthesia should be resorted to giving equal parts of olive oil and ether (3 oz each) in children and avertin in adults (60 mg per Kg body weight)

PULMONARY BLOOD VESSELS AND CIRCULATION

Kinetics of Respiration in Experimental Pulmonary Embolism were investigated by P S Megibow L N Katz and M Feinstein[4] (Michael Reese Hosp Chicago) From their results they conclude that respiration following embolism of major and moderately sized pulmonary arteries is characterized by tachypnea dyspnea and hyperpnea while that following embolism of pulmonary arterioles and capillaries is characterized primarily by tachypnea These changes are not dependent on anoxemia since onset of rapid breathing is not infrequently associated with an increase in the oxygen content and per cent oxygen saturation of the arterial blood Alterations in carbon dioxide content and in pH of the blood similarly play insignificant roles since hypercapnia is inconstant and when occurring is transitory while respiratory variations occur prior to any tendency to acidemia Actual decreases in volume and variations in elasticity in the lungs such as follow congestion edema and atelectasis while later adding definitive increases to the already accelerated respiration are by themselves not fundamentally implicated Evidence was obtained that the respiratory changes are not mediated centrally by circulatory slowing through the respiratory center The fact that bilateral vagotomy constantly converts rapid postembolic breathing into slow vagal breathing is utilized as further evidence that production of rapid breathing is peripheral rather than central The intimate rela

(4) A h I t Med 71 536 546 Ap 1 1943

tion of vascular obstruction to rapid breathing is pointed out and the fundamental mechanism with all varieties of pulmonary embolism is shown to be stimulation by distention of afferent nerve endings scattered throughout the pulmonary arterial bed, right side of the heart and superior vena cava Through rapid increases in elasticity of the lungs secondary reflexes are initiated altering the primary respiratory response, and these account for the absence of dyspnea and hyperpnea in military embolism A consideration of the therapeutics of postembolic respiration shows that of the drugs studied, only papaverine exerts any beneficial action There is a possibility that reflexes of similar origin may be responsible for dyspnea in congestive heart failure of the left side of the heart

Bronchial Factor in Pulmonary Embolism Joseph H Jesser and Geza de Takats (Univ of Illinois) visualized the bronchial tree of the dog and studied the effect of pulmonary embolism on its pattern In each instance the visible pattern of the main bronchi disappeared A bronchogram obtained five minutes after intratracheal injection of iodochloral showed the trachea and larger bronchi, including their finer branches well visualized Immediately after production of the embolus the second exposure was made The opaque material had been *squeezed into the terminal radicals The upper, middle* and lower main bronchi were not visible The third film taken eight minutes later showed little change, except more bullous dilatation of the finer bronchi and patches of emphysema as a result of incomplete bronchial obstruction without infarction In another experiment in which only the upper branches were visualized the same scattering of iodochloral was observed immediately 3 minutes and 10 minutes after the embolism was produced In the third set of films the typical pattern of the bronchial tree was shown again, before 3 minutes and 10 minutes after the embolism was produced Twelve

(5) Surgery 1 541 55 October 194?

experiments showed an identical pattern accompanied by the classic dyspnea and cyanosis of pulmonary embolism (Figs 13 and 14)

That disappearance of the main bronchi pattern is due to bronchial spasm is shown by the experiment in which this change in pattern was inhibited either by bilateral vagal section or by 1 35 gr atropine The spasm is not due to hyperpnea or anoxemia as mechanical obstruction to the trachea failed to produce marked

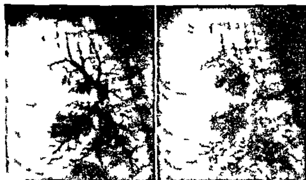


Fig 13 (left) —B f t t bel ject f 5 od bl al
Fig 14 (right) — F m n t ft nj t on

scattering of the opaque substance into the final radicals As vagal stimulation produces bronchial constriction and surgical or pharmacologic block of the vagus abolishes the bronchial spasm it can be assumed that reflex vagal impulses occur during pulmonary emoblism These reflexes may originate from hypertension in the pulmonary artery powerful myelinated receptors of the bronchial musculature congestion of the lung and pleural irritation

The authors have repeatedly stated that reflexes originating at the time of pulmonary embolism in man contribute to the causes of death and have suggested simple emergency measures for control Outside of oxygen

which is obviously helpful for cyanosis and dyspnea, intravenous injections of atropine (1/60 1/75 gr) and papaverine (½ gr) were recommended *The bronchial* asthma of pulmonary embolism explains the frequent finding of atelectatic areas in the x ray films of patients with pulmonary embolism The vagal stimulus produces not only bronchial constriction but also bronchial secretion The bloody mucous plug in the bronchi seen in patients dead from pulmonary embolism is the cause of atelectasis and patchy bronchopneumonia

Abdominal Pain in Pulmonary Thrombosis is reported by William S Middleton[6] (Wisconsin Gen l *Hosp Madison*)

Man, 54, was admitted with complaints caused by chronic infectious arthritis Signs of congestive heart failure on an arteriosclerotic basis soon dominated the clinical course. Under supportive measures, the circulatory balance was steadily being restored when he suddenly experienced excruciating pain in the lower part of the abdomen He became apprehensive, orthopneic and cyanotic, and the skin felt cold and clammy Despite immediate medical attention he became pulseless complained of continued pain had explosive vomiting and died within 20 minutes

Necropsy revealed no vascular occlusion in the abdominal *area or pelvis There was generalized arteriosclerosis,* involving particularly the aorta and coronary and renal arteries and arteriosclerotic calcification of the right and posterior aortic valve cusps Most significant, however was the extensive thrombosis of the pulmonary arteries The branch of the pulmonary artery to the left lower lobe was occupied by a firm, white thrombus and from this point there was extension of a red thrombus to the primary pulmonary artery Adjacent divisions were occluded by a dark red, nonelastic thrombus in which areas of lighter color appeared Histologic study of the lung disclosed only passive congestion slight hemorrhage and partial atelectasis

The dramatic crisis of abdominal pain and collapse marking the sudden occlusion of a large branch or branches of the pulmonary artery has been encountered by Middleton four times The attendant dyspnea and advancing cyanosis may lead to a correct interpretation

(6) Ann Int Med 18 345 49 March 1943

In one patient experiencing this sudden pain the simultaneous appearance of showers of fine moist rales in one base led to the accurate localization of the thrombus The explanation of abdominal pain in pulmonary thrombosis may perhaps be sought in de Takats Beck and Fenn s diagrammatic scheme of the neurologic impact of pulmonary occlusion

Treatment of Paroxysmal Pulmonary Edema with Special Reference to Forms Occurring under Wartime Conditions Aldo A Luisada[7] (Middlesex Univ) states that paroxysmal pulmonary edema occurs in many different conditions It may occur in soldiers sustaining skull injuries as in air crashes or car accidents or in sea warfare after penetration of water into the upper respiratory tract A third type is that caused by war gases Other types are those occurring in patients with tetanus poliomyelitis and subarachnoid hemorrhage

Two conflicting theories exist as to the origin of acute pulmonary edema The first deals only with attacks occurring in cardiac patients and explains them as due to sudden failure of the left ventricle The other embraces the pathogenesis of acute pulmonary edema of all types and states that the attack is the result of acute congestion of the pulmonary vessels followed by transudation in the alveoli The immediate cause of this condition is an intense stimulation of the vasodilator nerve of the lungs due either to a lesion of the nerve centers or to reflexes arising in various viscera The pulmonary edema in persons with skull injuries with subarachnoidal hemorrhage and with poliomyelitis is included in the first class as the lesion is central The pulmonary edema of drowning people and partly that of soldiers subjected to war gases should be included in the second class as reflexes arising in the mucosa of the larynx trachea and bronchi seem to be the main cause of the attack A multiple reflex probably occurs in hypertensive patients in whom the nerve receptors of the aortic arch

(7) Expe M d & S 1 30 J ry 1943

carotid sinus and heart wall are excited by distention A simpler reflex causing typical attacks may occur on stimulation either of the heart receptors (acute ischemia as in coronary occlusion) or receptors of the esophagus and abdominal organs

In accordance with these two theories, there are two methods of treatment The followers of the "heart failure" theory advocate stimulants, and those of the neurogenic theory advocate sedatives and narcotics Luisada believes that use of stimulating drugs in acute pulmonary edema is objectionable for the following reasons (1) Digitalis and strophanthin stimulate the right ventricle and consequently increase the pressure in the pulmonary vessels and by stimulating the vagus the digitalis glucosides promote narrowing of the coronary vessels (2) Drugs stimulating the vasomotor center tend to increase the peripheral resistance and thereby increase the severity of the left ventricular failure and of the pulmonary edema (3) Drugs stimulating the respiratory center tend to increase the frequency and depth of the respiratory acts This may increase the pulmonary edema by the mechanical action of suction increasing the transudation from the pulmonary vessels

On the basis of experimental and clinical experience Luisada recommends the following treatment in an attack of pulmonary edema using intravenous injections The physician should have ready several ampules of morphine (10 mg) atropine (0 5 mg) sodium phenobarbital (50 mg) papaverine hydrochloride (30 mg) and distilled water (10 cc) In hypertension, aortic regurgitation aortitis and pregnancy toxemia morphine plus atropine plus papaverine is the best combination In inhalation of toxic gases skull injuries, drowning and diseases of the central nervous system morphine plus atropine plus phenobarbital should be preferred If certain factors make intravenous injection inadvisable the three drugs may be injected hypodermically without further dilution Venesection may be useful if after a 10

15 minute interval the intravenous injection is not completely successful If the attack still continues a second injection should be given after 10 minutes Venesection is contraindicated in coronary thrombosis

Treatment with digitalis or strophanthin may prevent pulmonary edema in subacute insufficiency of the heart with weakening of the myocardium Preventive hypodermic injection of morphine plus atropine and phenobarbital should be given in all cases of traumatism of the skull In some cases of recurrent attacks of pulmonary edema the patient should receive at regular intervals tincture of belladonna and tincture of opium (solution of Magendie) by mouth 10 drops in the morning and 20 at night Oxygen has been used in prevention of pulmonary edema with good results

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PNEUMOCOCCIC PNEUMONIA

Epidemiology of Pneumonia Role of Type 14 Pneumococci in Producing Illness W G Smillie and Olga F Jewett[8] (Cornell Univ) attempted to determine the epidemiology of the pneumococcus in small children the place selected for study being a home for orphan children Routine cultures were made of nasopharyngeal material from all children in the medical wards Half the children were studied each week so that serial cultures were obtained for each patient at fortnightly intervals Cultures were made for all new children during the week following admission It a child developed pneumonia conjunctivitis purulent otitis media etc the secretions were cultured as soon as possible

Eighty per cent of 490 nasopharyngeal cultures were positive for pneumococcus Five hundred and forty six different strains were isolated indicating that some children harbored more than one strain Type 14 pneumococcus showed a prevalence of nearly 10 times the normal expectancy which compares closely with its prev

(8) Am J H Hh 3 987 995 pt mb 194

alence in previous series of actual cases of pneumonia in children under 2 years of age One third of the children with pneumonia and a similar percentage of children with other respiratory infections, but also a fourth of the normal children in the present series carried type 14 pneumococcus The focus of infection with type 14 pneumococcus was found to be a nursery from which most children were admitted Study revealed that 45 per cent of the children in the nursery carried a type 14 pneumococcus at one time or another Invasiveness of type 14 pneumococcus was studied under epidemiologic conditions after this nursery was closed to new admissions because of an outbreak of chickenpox Nine children remained in the nursery all had been carriers of type 14 pneumococcus at some time during the winter Gradually, the pneumococcus disappeared, so that when the nursery was reopened there were only three type 14 carriers in the group Thereafter every newly admitted child acquired type 14 pneumococcus within a month after admission Some picked up the infection at once

The studies suggest that a virulent strain of pneumococcus may enter a community permeate it, invade many individuals and linger for a considerable time without causing any apparent harm Some untoward factor may then enter the picture (such as an acute respiratory infection) which will lower the resistance of the carrier of the virulent pneumococcus strain to such a degree that the strain will invade the tissues of the body and produce a serious illness

Newer Knowledge Concerning Inception of Pneumonia and Its Bearing on Prevention is discussed by O H Robertson[9] (Univ of Chicago) Although the most frequent incitants of typical lobar pneumonia pneumococcus types I and II are not commonly found in the pharynx of healthy persons such individuals may become carriers on exposure to type I and II pneumonia particularly if they have a cold at the time The other

(9) Ann I t Med 18 1 14 J u ry 1943

30 odd types of pneumococci are found frequently, and often constantly, in normal throats as are staphylococci and to a lesser extent hemolytic streptococci and Pfeiffer s bacilli

Means by which pneumonia inciting bacteria gain entrance to the airways of the lung seem to be limited to inhalation of droplets and passage of fluid down the larynx Clinical and experimental evidence suggests that escape of infected fluid exudate from the upper respiratory tract past the epiglottis is much more important in inception of pulmonary infection than inhalation of bacteria containing droplets Much of the particulate matter in inspired air adheres to the mucous layer on the walls of the passages of the upper respiratory tract Further deposition takes place on walls of the bronchi This mechanism of air clearing is so effective especially in the case of dry particles that relatively few particles reach the alveoli Only when dust carbon or silica particles are breathed over long periods in high concentrations are they found in any quantity in air sacs The principal mechanism for expulsion of foreign matter from the lung is that of ciliary action which is capable of sweeping along particles at a rate of 0 25 to 1 cm per minute in the bronchi and up to 3 cm in the trachea The narrowing and widening of the diameters of the bronchi with each respiration possible peristaltic movement of the bronchi and cough aid in the eliminatory process via the trachea However when extraneous material enters the alveoli which contain no cilia or musculature elimination of foreign matter is much more difficult being limited to phagocytosis Liquids passing the barrier of the epiglottis tend to flow directly to the terminal airways depending on viscosity of the fluid and position of the body and are expelled much less easily than particulate matter As shown by Nungester and Klepser in rats chilling of the animal s surface temperature results in incomplete closure of the epiglottis

Robertson s experiments in dogs with pneumococcus

pneumonia showed definitely that spread to other lobes occurs from flow of infected exudate from the primary lesion via the bronchi and that secondary lesions may be artificially induced by deposition of such exudate in the trachea when the animal's position favors flow of fluid into the bronchi Primary lesions can be initiated in normal dogs by the same procedure Conditions necessary for inception of infection are implantation of micro organisms in the terminal airways obstruction to their elimination and local irritation or injury Further experiments indicated that local tissue irritation is more decisive than obstruction

Although it is not known how to prevent pneumonia following a cold, adequate care of the infection and awareness of the role of chilling and of the danger of acquiring the more highly pathogenic types of pneumococci from other individuals during exposure to crowds may aid in reducing incidence of pneumonia of this type The effect of gravity on flow of exudate in the respiratory tract and recognition of the influence of general anesthesia on closure of the epiglottis seem to provide some general indications for prevention of postoperative pneumonia Since sulfonamides have failed to prevent pneumonia in experimental animals such possibility is not likely in man However under conditions of a severe epidemic of influenza as the 1918 type such procedure may be advisable

Significance of the Gross Character of Sputum in Prognosis of Pneumococcic Pneumonia is discussed by Arthur W Frisch Alvin E Price and Gordon B Myers[1] (Wayne Univ) The gross character of rusty sputum in 651 cases of pneumococcic pneumonia was correlated with standard prognostic criteria and the outcome of the disease As a result of necropsy observations those patients who produced small amounts of viscid rusty sputum were classified as having "dry" lungs and those who raised large quantities of watery to gelatinous

(1) J Lab & Cl M d 8 1231 1237 J 1 1943

homogeneously rusty sputum were considered to have wet lungs and were put in that classification

In the former group the pneumonia was relatively mild while in the latter it was considerably more severe as shown by fatality rates of 6 and 23 per cent respectively as well as by significant differences in the number of pneumococci in the sputum extent of consolidation and incidence of bacteremia and leukopenia

It was concluded that the gross character of the sputum is of distinct value in prognosis of pneumococcic pneumonia It seems likely that the amount and gross character in pneumonia reflects the state of the lung copious wet sputum indicating an extensive area of inflammatory edema and a dry sputum a more localized lesion This hypothesis furnishes a plausible explanation for the high incidence of bacteremia and multiple lobe involvement in patients with wet lungs since the presence of a large edema zone would permit adequate opportunity for blood stream invasion or for metastatic spread to other lobes

While a greater number of wet lungs occurred in patients with advancing age and leukopenia the authors believe that these were accessory rather than primary factors determining the character of the pneumonic exudate The close correlation between the number of pneumococci and the nature of the gross sputum may be interpreted in two ways Possibly the outpouring of fluid into the alveoli represents an allergic response to the presence of a few pneumococci thus creating an environment which facilitates rapid multiplication of organisms but it seems more likely that the amount of exudate is directly proportional to the quantity of edema producing substance elaborated by the large numbers of pneumococci present in the lung The solution to this problem must await further study

Physiologically Directed Therapy in Pneumonia Alvan L Barach (Columbia Univ) describes measures

(2) A Int M d 17 81 819 No mb 194

including (1) administration of positive pressure (2) inhalations of helium oxygen mixtures and (3) inhalation of vaporized solutions of neosynephrin and epinephrine Narrowing of the bronchial lumen is frequent in pneumonias of undetermined origin, especially in the

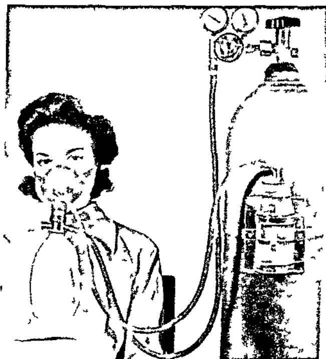


Fig 1 —Oxygen meter mask with attachment to water bottle to provide pressure during expiration

virus group Obstruction is due not only to bronchial spasm but to edema of the bronchial wall and accumulation of tenacious mucopurulent secretions in the small branches of the tracheobronchial tree Inhalation of oxygen enriched mixtures counteracts to a variable extent impaired diffusion of oxygen and irregular ventilation of the alveoli resulting in a decrease of the volume

of breathing lessened dyspnea and cyanosis When the obstructive factor in dyspnea is prominent inhalation of helium oxygen mixtures under positive pressure decreases the mechanical effort of breathing and helps maintain a patent airway Application of positive pressure to the inner surface of the lung also counteracts the tendency to edema of the lungs in lobar and bronchopneumonia Inhaling the sprays of the vaporized so

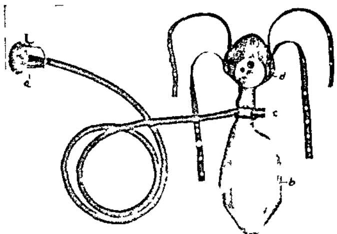
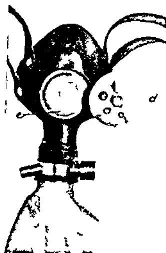


Fig 16 —a A mixe b coll ct g h g mergency i t k v l d adjuste f nt ol f e p t p u

lution of 1 100 epinephrine and 1 per cent neosynephrin reduces bronchial obstruction by stopping spasm of the bronchial wall loosening tenacious mucus and causing vasoconstriction of the mucous membrane of the tracheobronchial tree

The most effective method of administering positive pressure is by the helium oxygen hood in which the patient s head is enclosed by a hood with a transparent plastocele window Pressures of 1 to 6 cm water are maintained in both inspiration and expiration Positive pressure may be administered in expiration only

by use of a mask in which the exhaled air passes out through a tube immersed to a variable degree under water The injector mask which may be used both for administration of 40 to 100 per cent oxygen and also for inhalation of helium oxygen mixtures may be adapted for administration of 100 per cent oxygen under positive pressure of 1 to 5 cm water To accomplish this the expiratory valve is removed and an adaptor containing the rubber tubing put in its place (Fig 15) Under ordinary circumstances it is generally unnecessary to use pressures above 3 4 cm water Pressure may be gradually lowered by lifting the glass connecting tube from 4 to 3 and then to 2 or 1 cm water as desired The mask can also be used for helium oxygen mixtures It is better to admit a large flow of the mixture such as 7 10 L per minute on the oxygen regulator than to attempt to economize In oxygen therapy the collecting bag should be kept about half expanded at the end of inspiration but in administering helium oxygen for treatment of asthma there is even less resistance if the bag is kept almost full during both inspiration and expiration Inhalation of the vaporized solution of neosynephrin and epinephrine is best obtained by passing 5 L oxygen from a high pressure tank through a nebulizer in which has been placed 1 cc of a 1 per cent solution of neosynephrin and 0 5 cc of a 1 100 epinephrine solution



F 17 —d Adjuste f ontrol of exp r t ry p sure e p tory flutte v lve

Oxygen Mask Metered for Positive Pressure To the

mask just described Alvan L Barach and Norman Molomut[3] (Columbia Univ) added a mechanism which provides positive pressure during the expiratory cycle This consists of a series of apertures which are smaller than the diameter of the larynx When expiration occurs through a constricted orifice a positive pressure is reflected backward into the lung the extent of pressure being determined by the size of the orifice and the pulmonary ventilation When the largest opening is used there is little or no pressure during expiration The other orifices have been calibrated during quiet breathing in an adult having pulmonary ventilation of 5 5 L per minute so that pressures of 1 2 3 and 4 cm H_2O are obtained when the appropriate opening is used Within this dial is a flutter valve which prevents the outside atmosphere from entering the mask irrespective of the size of the opening on the outside of the dial In this mask an injector is attached to the oxygen tank to provide a measured concentration of oxygen in the inspired air A bag of light latex is used to collect oxygen being separated from the mask by an inspiratory valve which prevents rebreathing (Fig 16) Another addition is an emergency inspiratory valve which opens when the bag is collapsed Thus even if a shortage of oxygen occurs for a limited period no sensation of distress will occur since the inspiratory valve operates under minimal pressures

[Use of positive pressure gas therapy should take into consideration the mechanisms demonstrated by Drinker and Warren (this YEAR BOOK p 5) —Ed]

Modern Treatment of Pneumococcic Pneumonia Harrison F Flippin Leon Schwartz and Albert H Domm[4] report experience with 1 635 cases of pneumococcic pneumonia in adults treated with sulfapyridine sulfathiazole or sulfadiazine between August 1938 and April 1942 Gross mortality was 10 6 per cent which when compared with that of 40 1 per cent for 1 904 cases

(3) An I t M d 17 8 0 82 Novemb 194
(4) J A M A 121 30 237 J 3 1943

observed during five years prior to introduction of chemotherapy demonstrates the effectiveness of this form of therapy

Incidence and severity of toxic reactions following sulfadiazine therapy were less than those with sulfapyridine or sulfathiazole This difference consisted chiefly in lower incidence of gastro intestinal and renal manifestations associated with sulfadiazine therapy Sulfadiazine orally yields higher concentrations of the free drug in the blood and smaller proportions of acetylated drug in blood and urine than does sulfapyridine or sulfathiazole Furthermore acetylsulfadiazine is more soluble in urine than is acetylsulfapyridine or acetylsulfathiazole The differences in relative degree of acetylation and solubility of the acetyl derivatives appear to have an influence on incidence and severity of urinary tract complications following use of these drugs Finally higher concentrations of the drug are maintained for longer periods following intravenous administration of sulfadiazine than of sulfapyridine or sulfathiazole This is of decided value in control of the infection in certain types of cases On the basis of the foregoing data it appears that the drug of choice for treatment of pneumococcic pneumonia is sulfadiazine Except for the patient s age and other uncontrollable factors the length of time between onset of infection and beginning of specific treatment is the most important factor in prognosis Therefore sulfadiazine should not be withheld in mild cases and its use should not be delayed in a suspected case until signs of consolidation appear

The following plan of sulfadiazine treatment of pneumococcic pneumonia is suggested (1) early treatment (2) adequate chemotherapy with large initial dose smaller doses at regular intervals and continuation of drug until convalescence is established (3) maintenance of adequate urinary output (4) routine use of alkalis, (5) prompt recognition of drug toxicity, (6) determination of specific pneumococcus type, (7) use

of other therapeutic measures as necessary e g general supportive treatment type specific serum and surgical procedures

[New sulfonamides so far as tested do not show superiority over those in common use It has been demonstrated that when the drugs cannot be taken orally their sodium salts may be ad ministered conveniently and safely subcutaneously (Taplin G V Custer E A and Young L E *Journal of the American Medical Association* 121 313 315 Jan 30 1943) For example sodium sulfadiazine may be given in a 1 000 cc hypodermoclysis contain ing 5 Gm of the drug Penicillin is extremely effective against pneumococcus and the results of investigations now under way are awaited with great interest —Ed]

Sulfonamide Fast Pneumococci Clinical Report of Two Cases of Pneumonia and Experimental Studies on Effectiveness of Penicillin and Tyrothricin against Sul fonamide Resistant Strains are presented by William S Tillett Margaret J Cambier and William H Harris Jr[5] (New York Univ) From two patients having pneumonia and bacteremia strains of pneumococci (types I and VIII) were isolated which caused infec tions in mice that were totally refractory to treatment with sulfadiazine The clinical course of the patients and the clinical laboratory data (blood cultures and levels of sulfonamides in blood) also indicated the drug resistant characteristics of the infection Both patients responded rapidly and successfully to specific serum therapy

In experimental observations penicillin was found to be highly effective against infections in mice caused by either sulfonamide resistant or susceptible strains When tyrothricin (gramicidin plus tyrocidin) in single doses was used for treatment of mice protection was not uniformly complete against any of the strains How ever no evidence was obtained to indicate that sul fonamide resistance influenced the effect of tyrothricin

It was not possible to demonstrate that the drug re sistance of the patients strains was due to production of inhibiting substances In contrast cultures of an ad ditional strain of type I pneumococcus (MacLeod) were

(5) J Cli In t g t 49 255 M ch 1943

found to yield considerable amounts of the inhibitor

Relationship of Chemotherapy in Pneumonia to Persistence of Pneumococci was studied by William H Harris Jr[6] (New York Univ) in 47 patients with lobar pneumonia treated with sulfonamides Cultures of the pharynx were taken at frequent intervals during hospitalization and the results were correlated with the duration of specific sulfonamide therapy

In 55 3 per cent of the group sulfonamide therapy during the acute phase of the infection had no effect on the pneumococcus carrier state The remainder, 44 7 per cent, lost the pathogenic type pneumococcus during administration of the drug In 17 per cent, the pathogenic pneumococcus was lost after the drug had been discontinued, but before discharge from the hospital The others, 38 3 per cent, left the hospital carrying the pneumococcus responsible for their disease Pulmonary complications were frequently associated with a prolonged carrier state

Heterologous type pneumococci were recovered in seven instances following apparent disappearance of the pneumococcus type isolated on admission to the hospital

In so far as comparison with findings of earlier literature on the carrier state following pneumonia is possible it would appear that the convalescent carrier rate has not been significantly reduced by routine use of sulfonamides in pneumococcic pneumonia

Analysis of Pneumonia Deaths since Introduction of *Sulfonamide Therapy* J C Meakins and Richard D McKenna[7] (McGill Univ) review 21 fatal cases among 200 cases of pneumococcic lobar pneumonia seen in three years Mortality of 10 5 per cent is comparable with most published figures The ratio of males to females was proportional to incidence of the disease among the two sexes (3 1) All deaths (excluding infants) occurred in persons over 40 Average age in the fatal cases was 56 3 and that of survivors 36 1 All deaths occurred with in

(6) B ll. Johns H pki s H p 7 338 346 Ju 1943
(7) C d M A J 48 104 108 F b a y 1943

fections with the lower types of pneumococci Nine patients of 39 with type III infection died In four of these *there was proved bacteremia blood culture was negative* in one and not taken in four In general incidence of bacteremia among the fatal cases was striking Involvement of one lobe occurred in only 6 cases of two lobes *in 8* of three lobes in 4 and of four *lobes in 3 Mal*nutrition and associated diseases (of the cardiovascular system lungs kidneys liver or sinuses) were present in 90 per cent of those who died and in only 32 per cent of survivors No specific drug or serum was given in two fatal cases and two patients died 6 hours and two 26 hours after admission Combined drug and rabbit serum therapy was given in 4 cases In one the serum was given three hours after admission but in the others it was given late in the disease Seven patients died of peripheral vascular collapse (shock) for which no antishock therapy was instituted It seems justifiable since shock in lobar pneumonia is at least partly due to loss of plasma into the lungs to give antishock treatment early with peripheral vascular collapse and thus further lower mortality

Pneumonia Death Rate The death rate from pneumonia and influenza decreased to a new low in its last annual cycle September 1941 to August 1942 according to the Metropolitan Life Insurance Company [8] The average mortality rate for these diseases among the industrial policy holders was 21 per cent less than the previous low record of only a year before and 63 per cent less than the rate five years before Pneumonia and influenza are distinctly seasonal diseases and their 12 month cycle is shown in Figure 18 The upper curve represents the mortality rates for pneumonia and influenza combined reported in the 12 month period September 1936 to August 1937 while the lower curve represents the corresponding data for 1941 to 1942 The profile of the seasonal mortality curve has been

(8) St t t B ll M t p L f I u Co 3 8 10 N embe 194

changed almost beyond recognition The upper curve shows an extremely sharp peak in February, rising to more than 175 deaths per 100 000 on an annual basis In the lower curve although a maximum here also occurs during winter months the profile is relatively flat The

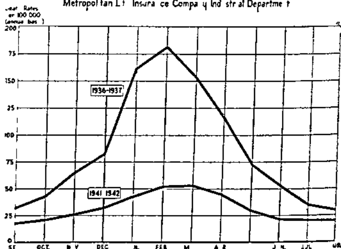


Fig 18

death rate over the winter months was about 70 per cent less than in the winter of 1936 1937

Cardiac Damage in Pneumonia Routine investigation of the cardiovascular system in patients with pneumonia led Otto Spuhler[9] (Univ of Zurich) to conclude that a considerable percentage of these patients show cardiac changes In a great many the cardiac damage is mild and consists of reversible inflammatory and parenchymatous changes of the heart muscle This myocardial damage is demonstrable on the electrocardiogram and roentgenographically (dilatation of the heart) Aside from these milder cases however, irreparable heart dam

(9) Schw i med Wchnschr 7 1099 110 Oct 3 194?

age occurs leading to permanent disturbances in the conductive system to bundle branch block and to marked dilatation of the heart Pericarditis originating by extension or by the metastatic route is a fairly frequent complication of myocardial damage in pneumonia Mural endocarditis is not uncommon but valvular endocarditis is rare

The myocardial damage is not influenced by any specific therapy Sulfonamides administered in the treatment of pneumonia have no effect on the course of myocarditis and do not prevent its recurrence This indicates that myocarditis in pneumonia is not of toxic but of inflammatory origin This viewpoint is supported by the fact that the cardiac changes are not related to the clinical severity of the pneumonia for persons with mild pneumonia may show considerable electrocardiographic changes whereas those with highly toxic pneumonia may exhibit only slight alterations on the electrocardiogram

OTHER BACTERIAL PNEUMONIAS AND PULMONARY ABSCESS

Staphylococcic Pneumonia Occurring during an Epidemic of Influenza Maxwell Finland, Osler L Peterson and Elias Strauss[1] (Harvard Univ) report on 66 cases of staphylococcic pneumonia encountered as a complication of influenza in the Boston epidemic of December and January 1940 1941 In every patient Staphylococcus aureus was obtained as the only or the predominant organism from cultures of the sputum or from the lungs or in pure culture from the blood pleural or other exudates or from multiple sources Symptoms suggesting pulmonary infection began the same day as those of influenza in one third of the cases and within five days in another third while in the rest they were delayed six days to three weeks There were 21 deaths (32 per cent) Blood cultures were positive for Staphylococcus aureus in 11 cases, in which 4 deaths occurred Pleural effusions were encountered in 15 cases — 9 with Staphylococcus aureus Virus studies indicated that influenza A played a role in this epidemic and in these cases The 66 cases were divided into six groups

In group 1 were seven cases of rapidly fatal pneumonia Clinical course was fulminant, the patients were semi stuporous had increasing dyspnea and cyanosis markedly increased pulse rate and rapid and shallow respirations Death occurred within five days after onset of pneumonia in six cases and on the ninth day in one Autopsies performed in four cases showed diffuse necrotizing bronchitis and bronchiolitis with numerous small and confluent abscesses around the bronchi and massive confluent areas of hemorrhagic and edematous bronchopneumonia In group 2 were six cases of fatal organizing and fibrosing pneumonia Clinical picture was similar to that in group 1 except that the patients survived 15 56

(1) A ch Int Med 70 183 05 August 194

days after onset of pulmonary symptoms Autopsies in four cases showed the bronchi dilated and filled with exudate and the walls necrotic and fibrosed There were numerous thick walled abscess cavities some of which communicated with the bronchi and bronchioles much of the intervening parenchyma was replaced by fibrous tissue Group 3 was composed of 11 cases of severe staphylococcic pneumonia with recovery The pneumonia was limited largely to one lobe or to one lung and im provement gradually occurred under intensive therapy with sulfonamides The patients were generally younger than those in the preceding group with exception of one being under 45 Pleural fluid was obtained in eight cases in five Staphylococcus aureus was obtained Two of the latter patients were treated by rib resection and in three the condition cleared up without surgical inter vention Group 4 included 18 cases of acute staphy lococcic pneumonia with rapid and complete recovery All but one patient received chemotherapy and all were markedly improved in 18 to 48 hours all but two were completely afebrile one to four days after admission Group 5 included a large number of cases of influenza and tracheobronchitis four of which showed Staphy lococcus aureus as the predominant organism in the sputum In these patients symptoms of influenza were associated with or followed by increased prostration hoarseness and severe cough accompanied by presternal soreness Close inspection of roentgenograms of the chest showed increased bronchial markings and some areas of fine mottling especially in the lower lobes Sulfonamides had no appreciable effect on the course Group 6 com prised miscellaneous cases of staphylococcic pneumonia Five patients had chronic cardiac disease one had bron chial asthma and all six died within 10 days One pa tient with pulmonary tuberculosis and three in whom influenza and staphylococcic pneumonia followed a focal infection recovered

During the period of the influenza epidemic 22 pa

tients were admitted with typical lobar pneumonia associated with the common types of pneumococci, who gave a history of influenza In 10 of these cultures of sputum showed Staphylococcus aureus in abundance, and 2 of the patients died

It seems important to bear in mind the possibility that both staphylococci and hemolytic streptococci may be associated with severe pulmonary complications of epidemic influenza It therefore seems advisable during epidemics of influenza particularly if cultures of sputum show that hemolytic streptococci or Staphylococcus aureus are unusually prevalent in individual patients or in a community to use sulfonamides in all cases of severe influenza In cases in which pulmonary complications have not become established a short course of treatment for two or three days should suffice

Abscess of the Lung Robert M Janes[2] *reviewed* 106 cases seen in Toronto General Hospital between 1933 and 1940 Grouping according to etiology of the lung abscess revealed that 30 per cent were the result of aspiration following tonsillectomy extraction of teeth other operations on the upper respiratory tract, general anesthetics and frank aspiration of material such as vomitus Thirty five per cent of cases were due to pneumonia and 22 per cent were recorded as idiopathic but a review of the histories suggested that the actual etiologic factor in these groups was nearly always aspiration of septic material Septic and sterile emboli were the cause in 10 per cent of cases The sequence of events which probably follows obstruction of a pulmonary vessel by a sterile embolus is extravasation of blood and fluid into the surrounding tissues with edema of adjacent bronchial walls and increase of intrabronchial secretions Such debilitated tissue forms an excellent culture medium for infective organisms A few abscesses of the lung (1 per cent) definitely followed an injury to the chest usually a severe blow or a crush One per

(2) Canad M. A. J 4 540 545 December 1942

cent of cases resulted from perforation of an adjacent lesion (esophagus or subphrenic) Cases complicating carcinoma or adenoma of the bronchus were excluded from this survey

Betts called attention to the close relationship between the bronchus and the blood vessels of a pulmonary lobule A bit of septic material lodging in such a bronchus causes first atelectasis of the small segment of lung supplied and later when the organisms gain a foothold thrombosis of the vessels This would explain the frequent finding of masses of necrotic material in these abscesses This means that all lung abscesses must be near some point on the surface of the lung and face chest wall mediastinum interlobar fissure or diaphragm Central lung abscesses are uncommon and probably occur only as a result of the breaking down of a neoplasm or from local ulceration around a large foreign body The most striking things about the bacteriology of lung abscess are the multiplicity of organisms found and the fact that each abscess contains more than one type of bacteria

Early treatment is similar to that of pneumonia including a trial of sulfonamide therapy which will not effect a cure but will improve the clinical condition owing to its effect on spreading infection in the surrounding lung tissue If a connection with a bronchus has been established and sputum is being produced postural drainage is in order Pneumothorax while occasionally accomplishing a brilliant cure is dangerous because of the possibility of empyema Less than 25 per cent of patients recovered spontaneously In general all abscesses not showing unmistakable evidence of recovery should be drained after five to six weeks and earlier if the clinical course is unfavorable Thoracoplasty is occasionally necessary to close large apical cavities that are not obliterated by drainage Chronic cases in which the abscess has become multiloculated secondary bronchiectasis has developed extensive fibrosis of the sur

tients were admitted with typical lobar pneumonia associated with the common types of pneumococci who gave a history of influenza In 10 of these, cultures of sputum showed Staphylococcus aureus in abundance and 2 of the patients died.

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Abscess of the Lung Robert M Janes[*] reviewed 106 cases seen in Toronto General Hospital between 1933 and 1940 Grouping according to etiology of the lung abscess revealed that 30 per cent were the result of aspiration following tonsillectomy extraction of teeth other operations on the upper respiratory tract general anesthetics and frank aspiration of material such as vomitus Thirty five per cent of cases were due to pneumonia and 22 per cent were recorded as idiopathic but a review of the histories suggested that the actual etiologic factor in these groups was nearly always aspiration of septic material Septic and sterile emboli were the cause in 10 per cent of cases The sequence of events which probably follows obstruction of a pulmonary vessel by a sterile embolus is extravasation of blood and fluid into the surrounding tissues with edema of adjacent bronchial walls and increase of intrabronchial secretions Such debilitated tissue forms an excellent culture medium for infective organisms A few abscesses of the lung (1 per cent) definitely followed an injury to the chest usually a severe blow or a crush One per

(2) Can d. M. A. J 4 540-545 December 19[illegible]

alent pneumonias are failure to obtain a history of exposure to birds failure to identify the virus of psittacosis and lower mortality Another reason for interest in psittacosis is the striking similarity and close antigenic relation between the agent of this disease and a number of other recently discovered viruses Some of these new viruses—those of lymphogranuloma venereum trachoma and inclusion conjunctivitis—have no constant or apparent relation to acute pulmonary infections Others were isolated from laboratory animals inoculated with materials from patients with atypical pneumonias or with influenza like infections Still others discovered as apparently normal inhabitants of the respiratory tract of certain laboratory animals are capable of inducing pulmonary lesions in those animals under specific experimental conditions Recent studies have indicated a wide spread occurrence of psittacosis or psittacosis like viruses in various birds all over the world Meyer has suggested the general term of ornithosis for these virus infections It is possible that certain aspects of this problem may have some significance for armed forces based in far off lands Iceland South Africa and Australia have figured in the recent reports on psittacosis

Like psittacosis Q fever is of considerable interest at present The agent of this disease is prevalent in Australia and has been isolated and identified in some of the western states of this country Definite evidence of infection with this agent has been found in certain cases with clinical features closely resembling atypical bronchopneumonias

Primary Atypical Pneumonias of Unknown Etiology—This type of pneumonia is probably a syndrome that may be produced by a number of agents It apparently exists sporadically and in small outbreaks Diagnosis can be made only by clinical and roentgenologic criteria—no one of which is specific—or by exclusion Distribution in the reported outbreaks has thus far been almost entirely limited to adolescents and young adults The

rounding lung tissue has occurred or the abscess cavity has become partially or completely epithelized cannot be cured by drainage alone These cases require lobectomy, the few instances in which both upper and lower lobes are involved require pneumonectomy

NONBACTERIAL PNEUMONIA

Virus Pneumonias are discussed by Maxwell Finland and John H Dingle[3] (Harvard Univ) *Pneumonias Associated with Known Nonbacterial Agents—Influenza, Psittacosis and Q Fever* —It is now generally accepted that some filtrable virus identical with or closely related to that originally demonstrated by Smith Andrewes and Laidlaw and later found by Francis was probably the causative agent in most widespread epidemics of typical influenza that have occurred in the past few years The virus has been labeled influenza A virus The findings in the recent epidemics indicate that under certain circumstances the influenza virus itself may set up a considerable bronchopulmonary reaction but that in most cases in human beings secondary infection with bacteria plays an important role and may alter the pathologic picture in the lungs Furthermore pneumonias may appear in patients with influenza during the height of the original attack or they may have their onset after a varying interval following apparent recovery from the influenza In the latter event it may not be possible to obtain the virus when the patient is first seen during the attack of pneumonia but serologic tests at that time may reveal a high antibody titer characteristic of patients convalescent from the virus infection

The present interest in psittacosis is due to the similarity of this disease to the atypical pneumonias that are now being encountered as far as symptoms physical signs roentgenologic and pathologic findings and course are concerned The outstanding differences in the prev

(3) New England J Med 2 24 350 Aug 7 378 385 Sept 3 1942

or homogeneous and denser near the hilus However it is rarely so dense and circumscribed as in pneumococcic pneumonia A number of variations in the roentgen picture has been noted A fairly well localized lesion may be found at the cardiophrenic angle there may be multiple small areas of soft infiltration or areas of diffuse coarse mottling—the disseminated focal pneumonia of Scadding which may be indistinguishable from tuberculosis

The course of the disease is generally mild but may be moderately severe or severe In the mild type the average febrile period is of seven or eight days duration *the defervescence preceding by lysis Ordinarily* the physical signs and objective evidences of illness are gone in two to three weeks The moderately severe type differs from the mild in that the patients feel and look more ill Progress of the disease is more rapid dyspnea and cyanosis may be present the fever persists longer and complications are more frequent In the severe form onset may be mild but the progress to a severe state is rapid Prostration dyspnea and cyanosis are present epistaxis chills sweating meningismus and coma have been described Roentgen examination of the chest reveals extensive involvement of a considerable portion of lung fields Moist rales and rhonchi are present however evidence of dense consolidation is not a rule Associated findings may be polyarthritis erythematous rash pleural effusion thrombophlebitis and myocardial and central nervous system involvement

The chief pathologic features in the fatal cases are those of a patchy hemorrhagic interstitial bronchopneumonia with acute bronchitis and bronchiolitis In two epidemics reported in infants acidophilic intracytoplasmic inclusion bodies were found in the bronchial epithelial cells in fatal cases and in cells obtained by swabbing of the throat of infants and adults having contact with these cases Cultures of sputum of persons with atypical pneumonia show the usual throat flora At

general consensus is that the disease is transmitted by contact but is not highly communicable The high incidence of infection in nurses and doctors supports the theory of contact spread and suggests that prolonged contact with patients may be necessary Onset in most cases is gradual and insidious over one day to one week or more Preceding or accompanying upper respiratory infections have been noted in 50 to 75 per cent of cases

The presenting symptoms are ordinarily quite uniform early in the disease regardless of the subsequent severity and course of the illness Fever cough, malaise headache and chilliness are almost constant complaints Temperature may be at any level between 99 and 105 F Cough is dry and extremely distressing and may occur in paroxysms which are difficult to control Substernal pain and soreness and tenderness of the abdominal muscles frequently result from tracheal irritation and cough The cough may be productive of mucopurulent blood streaked but not rusty sputum Shaking chills and rigor seldom occur Sore throat does not persist beyond the first few days of illness Some patients appear moderately or severely ill with prostration and occasionally dyspnea and cyanosis but most patients do not appear to be so ill as the fever and subjective complaints would warrant Pulse rate and respirations are normal and pulmonary signs if present are generally limited to fine or medium moist rales occurring late in inspiration The white cell count is usually normal

The first evidence of pulmonary involvement is usually obtained by chest roentgenograms The first change noted is an increase in size of one or both hilar shadows followed by an infiltration which extends outward from the hilus toward the periphery of the lung often in the shape of a fan or wedge and fades out gradually into the normal lung parenchyma The lesion is found most frequently in the lower lobe but it may occur anywhere Bilateral involvement is found in 20 per cent of cases Usually the infiltration is soft either mottled

both as to location and as to the progressive chronolog ical development, even of the various units in the cases in which they are multiple

The sequence of roentgen findings is as follows (1) An infiltrative process at onset (*a*) first progressively perbronchial from the hilus and then irregularly inter bronchial (*b*) customarily clearly definable as to limits



F g 20 —C tton wool ppe ll d ra ph olution with w n t d l p g f m ght ppe h l

despite its disregard for segmental or lobar structural limits usually involving more than one segment and fre quently parts of more than one lobe (2) Quickly ac companied by a cotton wool appearance of multiple areas of partial or semiconsolidation (*a*) scattered through the area of infiltration and usually distributed in radial progression also (*b*) frequently subsequently (6 24 hours) coalescing (*c*) occasionally eventually (20 48 hours) filling approximately a whole lobe to simulate lobar pneumonia but always managing to present a striated infiltrative type background rather than pure

tempts to isolate viruses have not brought conclusive results Treatment of atypical pneumonia at present is entirely supportive or symptomatic The various sulfonamides have no effect and in some cases materially increase the discomfort of the patients

Virus Pneumonia Roentgen Characterization of Recent Virus Pneumonitis with Bronchopneumonia On



F g 19 —Cotton wool appea f cent lly loc ted e ly i filtrat n nd p t l co sol dat on

the basis of 221 cases Asa E Seeds and Morton L Mazer[4] (Baylor Univ) feel that there are several roentgen characteristics of atypical pneumonia other than inconstant *peculiarities in distribution a few of these* seem to be almost exclusive Though the roentgen peculiarities of this syndrome do follow the nonlobular nonsegmental and inconstant distribution pattern this pattern is followed in a more or less orderly manner

(4) Am J Roentg ol 49 30 38 January 1943

produced by such incipient changes as those which characterize the early onset of this syndrome the roentgen diagnostic procedure has acquired a position of primary importance

Primary Atypical Pneumonia, Etiology Unknown, was studied at Camp Claiborne La where an unexpectedly high incidence of pneumonia occurred during the summer 1941 A commission composed of John H Dingle Theodore J Abernethy George F Badger G John Buddingh A E Feller Alexander D Langmuir James M Ruegsegger and W Barry Wood Jr [5] made clinical studies on 69 cases and abstracted 216

FREQUENCY OF OCCURRENCE OF SYMPTOMS IN 69 CASES OF PRIMARY ATYPICAL PNEUMONIA ETIOLOGY UNKNOWN

	Symptom	Cases No	%
Onset	Gradual	51	74
	Sudden	18	26
Constitut onal symptom	Feverishness or fever	56	81
	Headache	54	78
	Malaise	5	77
	Chilliness without rigor	ᴗ2	75
	R gor	9	13
Symptoms referable to the respiratory tract	Cough	68	99
	Coryza	28	41
	Sore throat	25	36
	Sputum		
	Nonbloody	36	5°
	Blood streaked	8	12
	Thorac c pain		
	Substernal	17	26
	Pleural	1	18
Total number of cases		69	

B ed on 66 ca s

cases from hospital records Characteristics of atypical pneumonia were those of mild to moderately severe illness of gradual onset in which constitutional symptoms predominated over symptoms referable to the respiratory tract in the early stages Physical signs of involvement of the lungs were ordinarily minimal although there was x ray evidence of pulmonary infiltration Compli

(5) W M d S 23 248 M h, 1943

homogeneity, (*d*) usually establishing a fixed distribution for any one area in two or three days, which afterward behaves as a "unit" (3) Beginning of resolution or absorption (*a*) generalized and uniform progressive loss of density throughout the "unit" (*b*) development of an appearance of "wire grass" infiltration or 'pseudofibrosis' (suggesting a simple inverse of the developing



Fig 21—Early wire grass type infiltration characterizing midresolution

process) (*c*) eventual progressive complete clearing of this process in 5 to 14 days usually 5 8 days in cases of single "units" (4) Occasional development of multiple units with (*a*) subsequent definite dates of onset and individual chronology (*b*) rarely involving nearly all visible parts of the lung (*c*) usually no one unit disturbing the approximate prearranged chronology of any forestarted unit (5) Occurring quite typically in children (under or over 2 years)

Owing to the evident difficulty in clinical diagnosis

cific organism In only 12 per cent of cases were the patients severely ill Duration of the illness varied greatly the shortest recorded was 2 days and the longest 45 days and in most cases it lasted 7 days

During the period of investigation 34 cases were observed in which illness was indistinguishable from atypical pneumonia except for lack of x ray evidence of pulmonary infiltration These cases have been called bronchitis resembling atypical pneumonia Symptomatology of other infections of the respiratory tract



Fg 2 (left) —C 1 I t t t l pneumo a l em t of al e l w lls I h m t xyl n-e n d d from × 95
Fg 23 (ght) —S m s P d m nce f m yt ells lve i ept I n h m to yl n eo d ed f m × 130 (S ph p 6)

likewise did not show any significant differences from that of atypical pneumonia

One death occurred among the 285 cases Findings were those of hemorrhagic interstitial bronchopneumonia acute bronchitis acute follicular splenitis and mesenteric lymphadenitis Additional pathologic information was obtained bronchoscopically in 10 patients with atypical pneumonia The bronchi of the involved lobes showed an acute inflammatory reaction of the mucosa with considerable congestion The secretion was mucoid to mucopurulent

Clinical and epidemiologic evidence is consistent with the hypothesis that atypical pneumonia is an acute in

cations were rare and prognosis was excellent History of exposure to cold and dampness before onset was encountered in 42 per cent 35 per cent of the patients gave a history suggesting a preceding respiratory infection There was no consistent history of insect bites or of contact with birds or animals

Frequency of occurrence of symptoms in the 69 study cases is given in the table Physical chest signs were scanty *Differences in excursion of the chest* were noted in a few cases Dulness was observed in less than half Pleural friction rub was not encountered in any case The most characteristic finding was subcrepitant and sticky' rales, best elicited by cough and deep breathing *and occurring in showers near the end of respiration* Musical rales of a coarser quality and rhonchi were heard in about 40 per cent Other significant physical signs were not noted

Roentgen appearance of the lesions was rather characteristic At onset there was increase in the hilar shadow uni or bilaterally Perihilar infiltration became increasingly apparent in subsequent plates and the shadow then extended toward the periphery of the pulmonary field in either a wedge or a fan shape A common site was one or the other cardiophrenic angle In some instances the process appeared to be confined to a local area such as a portion of an upper lobe in others diffuse seeding of one or both pulmonary fields occurred In still others infiltration extended along a septum The infiltration usually appeared to be soft and either patchy or homogeneous greatest density was near the hilus Usually the lesion underwent slow resolution in one to three weeks One of the lower lobes was most frequently involved multiple lobar involvement occurred in 10 per cent

Leukocyte counts and differentials were essentially normal Bacteriologic examination of sputum material obtained by swabbing the throat and blood from patients with atypical pneumonia failed to reveal a spe

of interstitial pneumonia In severe cases however the interstitial changes spread and the alveoli become involved The exudate differs from that of lobar pneumonia or bronchopneumonia in that it consists mostly of mononuclear elements The hyalin like ring forming the inner lining of many alveoli is characteristic and explains the severe cyanosis and fatal outcome of the disease in some cases No virus studies were made in the present cases The lining cells of the bronchi in the first case showed few eosinophilic inclusion bodies which though spherical were not surrounded by a halo as described by Adams in virus pneumonia Although there is no proof that the pneumonia in the two cases was caused by a virus failure to demonsrate a bacterium involvement principally of the interstitial tissue of the lungs and the cytologic elements of the inflammatory regions make it likely that the disease was due to a virus

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UNCLASSIFIED PNEUMONIA

Silent Bronchopneumonia Paul M Andrus[7] (London Ont) reports on 96 cases of acute pulmonary exudation observed in a military district since the outbreak of war and which would presumably have escaped detection had it not been for routine roentgen examination resulting from war conditions The films showed bronchopneumonia like shadows of mild to substantial extent and intensity Investigation showed that the persons concerned were not ill but most of them admitted a present or recent cold or flu Occasional cases were entirely silent in this respect No crepitations were heard by auscultation but the respiratory lag of the affected side was usual Erythrocyte sedimentation rate was elevated without exception (35 115 mm with 200 mm tube) Leukocyte counts were elevated (12 000 35 000)

Fifty four per cent of the lesions occurred on the right side of the thorax Seventy six per cent were predomi

(7) C M A J 4 339 344 Octobe 194

fectious disease transmissible by contact from person to person and that unrecognized and inapparent infections exist and may constitute the effective source of spread of the disease No specific bacterium, fungus or rickettsia has been related etiologically to the disease in the present series There was an incidence of high complement fixation titers with meningopneumonitis virus in Negro patients this may perhaps be attributed to the cross-reaction between this agent and that of lymphogranuloma venereum

Pathologic Changes in So Called Atypical Pneumonia Otto Saphir[6] (Michael Reese Hosp, Chicago) reports the pathologic findings in the lungs in two cases of possible virus pneumonia



Fig 24 —Case 2 In ol em nt f s pta monocyt a d f w polymorphonucl l uk yt within alve li hyal n l ke g lining inner w ll f on alveolus Giemsa stain educed f om × 130

The first case (Figs 22 and 23) was that of a girl 3 who was admitted with abdominal pain and a diagnosis of appendicitis but began to cough became cyanotic and died shortly after admission The second case (Fig 24) was that of a woman 29 in the eighth month of pregnancy who was admitted with symptoms of an irritating cough cyanosis and parasternal pain of one day's duration The next day she was placed in an oxygen tent without relief Despite heroic measures she died the second day of hospitalization

The basic pathologic lesion in this condition is an interstitial pneumonia characterized by monocytes lymphocytes and a few red blood corpuscles It is likely that most pneumonia epidemics which have an extremely low mortality rate are comprised almost exclusively of cases

(6) Radiology 40 339 343 April 1943

characterized by focal pulmonary roentgen shadows which appear suddenly and disappear without producing any appreciable clinical symptoms Most cases are discovered on routine mass roentgenography Loeffler described several forms (1) large irregular not sharply defined shadows which may occupy a considerable portion of the lung field (2) a small round shadow (3) multiple small shadows in one or both lung fields (4) foci sharply defined at the margins of a lobe and (5) shadows in the vicinity of the hilus simulating hilar enlargement Another prominent feature is eosinophilia of the blood varying from 6 to 60 per cent This appears simultaneously with the infiltrate but may persist much longer than the latter The patients are mostly afebrile and only occasionally complain of slight malaise fatigue and irritating cough Physical signs are wanting there may be minimal dulness enhanced vesicular breathing few crepitant rales or friction rub

The eosinophilia suggests an allergic nature of the condition Ascaris lumbricoides has been implicated by some After ascaris eggs have been ingested the parasites do not immediately develop in the intestinal canal but the larvae penetrate the intestinal wall and invade the lungs via the blood stream from there they apparently find their way back into the intestine where they mature Presumably the toxins of the parasite produce a hypersensitivity and the larvae during their stay in the lungs give rise to an allergic inflammatory reaction in the form of an exudate

The fleeting infiltrates may be confused with early tuberculous infiltrates In the latter condition however though the patient may recover clinically after a few days he soon exhibits a recurrence of fever malaise and increased sedimentation rate Likewise eosinophilia is rare in frank tuberculous infiltrates Both the fleeting eosinophilic infiltrate and early tuberculosis may be confused with many conditions giving a similar x ray shadow such as the fleeting infiltrates of childhood tuber

nantly in the lower lobe, 8 per cent in the upper lobe and 16 per cent in the midlung zones As in manifest bronchopneumonia distribution of the shadow tended to occur within a cone shaped segment, with apex toward the hilus Roentgen shadows disappeared and the sedimentation rate became normal in one to five weeks Some residual abnormal pulmonary or pleural shadow, slight or marked remained after resolution of the pneumonia in 38 per cent In two cases presence of bronchial dilatation was subsequently proved by use of iodized oil A useful number of bacteriologic examinations was not made These cases of silent bronchopneumonia were considered to be due to a low grade virulence or to be cases in which diagnosis was accidentally first made in the post toxic stage but before completion of resolution of exudate

The practical importance of silent bronchopneumonia is evident Because of the frequency with which this type has come to light by the accident of survey roentgenography it follows that such disease may and probably does occur regularly among the civilian population Lacking roentgen study it is safest to regard and manage all cases of intercurrent respiratory disease as possible cases of bronchopneumonia Confinement to bed, even of mild cases until all symptoms subside confirms the public health viewpoint If it is not feasible to x ray the chests of all such persons when symptoms have subsided the clinician has a less expensive guide to exudation in the erythrocyte sedimentation test Of great practical importance also is the fact that chronic basal injury of the bronchiectatic type can and does result from silent unidentified bronchopneumonias as from clinically manifest ones

Transitory Eosinophilic Lung Infiltrates R Staehelin[8] (Univ of Basel) states that this condition repeatedly reported by Loeffler between 1931 and 1936 is

(8) S hwei med Wchn ch 72 785 789 J ly 18 194
(8a) Ibid pp 809 811 July 5 1942

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culosis (perilular infiltrate epituberculosis perifocal in flammation in primary lesion) fleeting shadows of atypical lobar and focal pneumonias beginning lung abscess and local atelectases

H v Meyenburg (Univ of Zurich) on the basis of postmortem examination in four cases discusses the pathology and pathogenesis of fleeting eosinophilic lung infiltrates Three of the patients died immediately after injury and one died of fulminant tetanus The macroscopic aspect of the pulmonary foci was not characteristic or pathognomonic They were focal pneumonias of varying form extent and localization the foci were round wedge shaped rosette shaped as in bronchopneumonia or infarctoid *Microscopically all had in common a high grade eosinophilia of the inflammatory exudate* Other cellular elements of the exudate included some plasma cells lymphocytes and desquamated alveolar cells Giant cells seemingly derived from confluent alveolar cells surrounding a small vacuole were a constant finding In two cases there was also eosinophilic bronchitis and bronchiolitis indicating the *bronchopneumonic distribution of the lesions In one case* there was a necrotic focus in the *midst of the* pneumonic infiltrate in the center of the focus were necrobiotic leukocytes surrounded by nonidentifiable dead cells and peripheral elements resembling epithelioid cells Charcot Leyden crystals were found in one of the pulmonic infiltrates Eosinophilia of the blood and bone *marrow was present in all cases In two cases eosinophilic infiltrates* were also found in the liver

The etiology of fleeting pulmonary infiltrates could not be clarified in the present series of cases Bacterioscopic examination gave negative results except in the case of tetanus in which diplococci probably pneumococci were *discovered in the air passages and lungs* No *tubercle* bacilli were found in the aforementioned necrotic focus Although two patients harbored a few ascarides in their intestine no larvae could be found in

their lungs A possible allergic history which may have been of some significance was elicited in two cases

Fleeting eosinophilic infiltrates of the lung constitute in all probability an allergic response to various antigens which may reach the organism by various routes The finding of eosinophilic infiltrates in the liver in two cases of the present series and in the epididymis simul taneously with the appearance of the infiltrate in the lung in another living patient indicates that the infil trates are not necessarily limited to the lungs

Chronic Pulmonary Eosinophilic Infiltrates The fleet ing type of pulmonary eosinophilic infiltrates has been designated as the Loffler type In 1940 another type was described independently by Lohr and by Leon Kindberg and collaborators Their patients presented a severe rather septic clinical picture with a course of several months duration M Kartagener[9] (Univ of Zu rich) describes a third type of pulmonary eosinophilic infiltrates characterized by chronicity and mildness of clinical symptoms

Woman 40 with a negative history as to previous attacks of asthma or asthmatic bronchitis complained of vague pains in the chest and back Roentgen examination revealed small focal chronic infiltrates in the right upper pulmonary field These have persisted over 15 month Blood eosinophilia al though varying in intensity from 10 to 34 per cent was con stant during this period Apart from occasional attacks of subfebrile temperatures night sweats backache and headache the patient showed no signs of any disea e and surely not of a severe wasting illness

Thorough investigation excluded constitutional eosinophilia and the presence of lymphograuloma or echinococcus The stools yielded no ascarides The sputum contained varying amounts of eosinophilic leukocytes Repeated examination for tubercle bacilli gave negative results as did animal inoculations In view of a strongly positive Pirquet reaction old hematoge nous foci of pulmonary tuberculosis (possibly reactivated) cannot be excluded with certainty The constant eosinophilia in blood and sputum however militate strongly against this possibility

(9) S hw m d W hn h 7 86 864 A g 8 194

It is assumed that all three forms of pulmonary eosinophilic infiltrates are but variants of an allergic syndrome based on the same pathogenesis but with a multiplicity of causes

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TUBERCULOSIS

Experimental

Survival of Tubercle Bacilli in Books was investigated by C Richard Smith[1] (Barlow Sanatorium, Los Angeles)

Artificially or naturally positive sputum was smeared in 0 05 cc amounts on 1 in squares cut in but not removed from the leaves of books The books were immediately closed while the pages were still wet and stored in a dark cupboard in an unheated room In another experiment the pages were smeared over an area 2 × 3 in with cotton swabs dipped in a watery suspension of tubercle bacilli Some of the leaves were exposed to unfiltered northern roomlight

The results were in agreement with those of a previous experiment with tubercle bacilli deposited on glass cover slips In both instances proved survival at room temperatures was not more than a few days in roomlight and from less than 2 weeks to about 3½ months in the dark the period of recoverability was longer when the dose deposited was increased during the winter season when average temperature and relative humidity were lowest and by animal inoculation Survival was definitely longer in naturally positive than in artificially positive preparations Printer s ink had no unfavorable effect on survival since bacilli lived as long on printed as on blank paper They lived a relatively short time on bond paper which fact must be attributed to some characteristics of the paper itself

A questionnaire distributed to all patients of the sanatorium revealed that occasional uncovered coughing

(1) Am R v T b c 46 19 559 N mb 1942

into books was fairly common among them whereas thumb wetting occurred but was infrequent

Smith concludes that books and magazines used by sputum positive patients are possible sources of infection A simple and effective method for rendering contaminated books noninfectious is their quarantine for one month During this period they should not be read by nontuberculous patients student nurses or members of the sanatorium staff and perhaps not even by sputum negative patients

Correlation between Anatomic Changes and the Allergic State in Tuberculous Guinea Pigs C Eugene Woodruff and Ruby G Kelly (Northville Mich) infected 218 guinea pigs subcutaneously with 0 1 mg virulent tubercle bacilli and tested them at intervals of two or three weeks to follow the changes in skin sensitivity The tests were made subcutaneously using 0 1 ml tuberculin made up in tenfold dilutions varying from 1 10 to 1 10 000 O T Generally the animals were allowed to die of their disease only few of the highly allergic pigs being killed as controls

The animals frequently showed a spontaneous deterioration of their allergic state as indicated by a low level of skin sensitivity Of 33 animals with a sensitivity below the 1 mg level before death 31 showed extensive pulmonary lesions containing large numbers of acid fast bacilli and the remaining 2 showed a few bacilli in the lungs In the animals which lost most of their allergy before death the pulmonary lesions were characterized further by absence of caseation Many of the alveoli were packed with polymorphonuclear or mononuclear cells containing tubercle bacilli but there was little or no necrosis of the alveolar walls The second finding which characterized the anergic animal was epithelioid cell infiltration throughout the splenic pulp and frequently infarction of the organ There were few or no acid fast bacilli in the pulmonary lesions of 91 animals

(2) J Imm ol 45 79 85 O t b 194

which were at or above the 0 1 mg sensitivity level at the time of death Occasional tubercles in these animals had caseous centers but even in the caseous material only a rare tubercle bacillus could be found

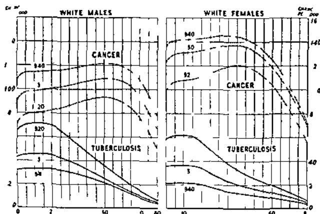
Effect of Low Oxygen Tension on Development of Experimental Tuberculosis Arnold R Rich and Richard H Follis Jr found that when animals were kept continuously in a chamber exposed to an oxygen content not higher than 9–10 volumes per cent, development of experimental infection was markedly inhibited in comparison with the controls kept in open cages in the same room That inhibition was due to low oxygen tension and not to other factors operative in the chamber seems clear from the fact that in one experiment in which the oxygen content in the chamber was kept at 20 volumes per cent (i e that of atmospheric air) all other conditions being equal there was no difference whatever between the chamber animals and those kept in open cages Furthermore when the oxygen content was kept at 12 to 14 volumes per cent the inhibitory effect was greatly diminished

The experiments support the view that low oxygen tension can be an important factor in the beneficial effect of collapse therapy in pulmonary tuberculosis They likewise support the view that the relative anoxemia of *the fetus is a factor in its resistance to tuberculous in*fection They offer however little support for the view that decreased oxygen tension in the atmospheric air at high altitude resorts can inhibit significantly the activities of the tubercle bacillus at least not at the altitude at which sanatoriums are situated for it required a much lower oxygen tension to effect the infection in the present experiments It is conceivable that the lowered oxygen tension in the air acting in conjunction with the low oxygen tension in a lung subjected to therapeutic pneumothorax may exert a deleterious effect on the tubercle bacilli in the collapsed lung

(3) B ll Joh H pk s H p 71 34 363 D c mber 194

EPIDEMIOLOGY AND CONTROL

Cancer and Tuberculosis—A Contrast[4] Figure 25 shows the chances of eventual death from tuberculosis and cancer according to health conditions in the general population of the United States in 1920 1930 and 1940 the curves relate to white persons only The greatest probability of eventually dying of tuberculosis is found



Fg 2 —C t g h n f nt l d th f m n nd tube ul n th U t d t t n 19 (193) d 1940

at ages 5 15 Peak values in 1940 were 33 per 1 000 for males and 21 per 1 000 for females In the curves for cancer the peaks come much later in life at the age of 50 for males and 35 for females with about 120 and 150 chances per 1 000 respectively for 1940 The chances of eventual death from cancer are markedly higher for females at all ages except 65 and over the risk for tuberculosis is greater for males Whereas the chances of eventual death from cancer or tuberculosis were practically equal for the new born male of 1920 the divergence in the trend of mortality from these two conditions since then has been so great that by 1940

(4) St t t Bull M t op I f I C 3 A gu t 194

cancer presented a hazard 3½ times greater than that of tuberculosis For new born females the chances of eventual death from cancer in 1920 were only 1⅔ times those from tuberculosis, by 1940 they were 6½ times as great

Simplified Procedures in Tuberculosis Control The urgency of the times requires elimination of every unproductive procedure in the tuberculosis control program if the tuberculosis administrator and health officer are to meet the increasing demands for clinic service in the face of decreasing personnel The principles adopted by the Bureau of Tuberculosis of the Department of Health in New York City with unquestioned success are presented briefly by H R Edwards and A B Robins[5]

All patients receive a posterior anterior chest roentgenogram at the time of initial admission and at each periodic supervisory visit Paper film is used routinely All new patients and those who require additional information are studied fluoroscopically Physical examination is used only when symptoms or x ray findings suggest pulmonary disease A complete folder type record is made out only for patients with symptoms highly suggestive of pulmonary disease For all others cards are made out All x ray films are interpreted according to a numerical code

Patients with active cases are hospitalized forcibly if necessary Those with questionably active cases are seen at frequent intervals those with arrested cases at 6 month intervals for 18 months, those apparently cured at yearly intervals for 3 years and patients with pleurisy at 6 month intervals for 5 years Contacts are divided into four groups (1) Infants are tuberculin tested and radiographed and if negative retested every six months as long as they remain in contact with the source case If the Mantoux test is positive they are re x rayed every six months until the age of 3 when unless there is

(5) Am J Pub He lth 33 517 5 5 May 1943

evidence of an active tuberculosis they are discharged (2) Children between 3 and 10 are not tuberculin tested but are x rayed and discharged if the findings are negative (3) Adolescents and young adults with a history of exposure prior to or during adolescence are tuberculin tested The negative reactors are discharged In positive reactors and those still exposed to persons with an open case supervision is continued to the age of 25 (4) Adult contacts are supervised for two years at six month intervals Persons in susceptible groups i e such as those whose susceptibility is related to age racial stock economic status character of employment etc are subjected to mass x ray examination

Records of cases with pathology are retained in the clinic for three years after supervision has been discontinued then abstracted on a card and transferred to a central storage unit The x rays are photographed on 35 mm microfilms Negative x rays are destroyed after the diagnosis has been entered on the corresponding card

[Such simplification s based largely on knowledge of the behavior of tuberculosis in the population in general the principles are sound However its weakness is in not providing adequately for detection and timely treatment of cases which develop atypically See Brailey this YEAR BOOK p °61 —Ed]

Pulmonary Tuberculosis with Cavitation Clinical and Epidemiologic Features and Case Fatality Brian C Thompson[6] reports on 406 patients (211 males and 195 females) with pulmonary tuberculosis and positive sputum the group included every patient over the age of 10 with this type of disease known to a county dispensary in a mining area between 1928 and 1938 Previous contact with persons with proved sputum positive tuberculosis was established in 148 cases (36 5 per cent) Contact tended to have occurred more frequently in the younger patients

Cough was the principal symptom causing 41 1 per cent of the patients to seek medical advice Asthenia in the form of toxemic symptoms such as malaise weakness

(6) Tube cl 3 139 150 J n 194

lassitude or languor was presented by 16 7 per cent and was more common in females than in males Chest pain was complained of by 13 5 *per cent* and *predominated* among males A history of recent hemoptysis was given by 13 3 per cent Phthisis was diagnosed during or as a direct result of an acute febrile illness in 3 4 per cent mostly as the result of influenza Hoarseness, sore throat or dysphagia was presented by 3 2 per cent, and loss of weight was complained of by 3 per cent Twelve patients sought medical attention because of abdominal symptoms such as indigestion pain in the loins, diarrhea, melena and anal fistula Only 2 per cent complained of shortness of breath and only one patient of night sweats

Less than one fourth of the patients had symptoms of less than three months duration nearly one half had been consciously ill for more than six months and one fifth for over a year In some cases the private physician had neglected to investigate adequately symptoms which deserved attention and some patients were even obliged to consult a second practitioner to obtain a recommendation to the dispensary This indicates that the delay was not invariably due to the patient s negligence Younger patients tended to give a shorter history than older patients and males tended to give a shorter history than females Patients with a history of contact sought advice earlier than those with no known contact

The early case fatality was particularly striking 42 per cent of the patients dying within 12 months of diagnosis At the end of the first five years three fourths of the original total were dead and half of the survivors died within the second five years In other words of any eight patients with positive sputum two would be expected to survive 5 years and one to survive 10 years There are indications that these high fatality rates are not exceptional for an industrial community of the type under consideration and therefore the discovery of tubercle bacilli in the sputum is of grave prognostic significance In this series the expectation of life for a

patient whose initial symptoms include hemoptysis is shown to be more than twice as good as that for other patients

Development of Tuberculosis in the Apparently Healthy Adult was investigated by Arthur B Robins[7] (Dept of Health New York City) Incidence of tuberculosis was determined by re x raying a group of home relief recipients whose previous films had shown no evidence of pulmonary tuberculosis There were 8 731 persons 86 2 per cent of whom were Negroes and the average interval between the two x ray examinations was 14 2 months Twenty five cases of tuberculosis were found in this series 24 of chronic pulmonary tuberculosis and 1 of idiopathic pleurisy with effusion Average age for all subjects was 33 3 Over two thirds of the cases occurred in individuals over 30 Eighteen of the 24 pulmonary lesions were considered exudative or caseous pneumonic and the remaining 6 productive In 18 patients the lesion was in the right lung and in 5 in the left lung in 1 it was bilateral Eleven of the 13 cases in females were right sided whereas 7 males had lesions on the right 3 on the left and 1 on both sides

A history was obtained in 16 cases In only 2 was the contact history definite and of consequence in 11 it was negative Only 9 patients gave a history of symptoms prior to discovery of their lesions by x ray Seven patients among the 18 whose present status is known died All were Negroes The interval from first diagnosis to death averaged 5 months in the two males and 9 2 months in the five females Incidence of tuberculosis in the entire group was 2 9 per thousand 1 3 per thousand in whites 2 8 per thousand in Negroes and 6 6 per thousand in Puerto Ricans Annual incidence rate in the group as a whole was 2 4 per thousand Study of a sample of over 4 000 individuals who failed to return for a second x ray examination by checking their names against the central roster of reported cases and the

( ) Am R Tub 47 1 10 J ry 1943

register of deaths from tuberculosis revealed an inci dence of 2 2 per thousand Comparison of the annual incidence rates in the predominantly Negro home relief population of Harlem with the rates in white groups of higher economic level did not reveal marked differences

The study has led to the conclusion that the annual incidence rate is not determined by the mortality rate Incidence and mortality are independent of each other and their resultant is the prevalence Attempts to link the three factors through application of rigid artificial formulas only lead to confusion and contradictory re sults

PATHOGENESIS AND DEVELOPMENT

Tuberculosis of Mixed Localization Oscar P Agui lar, Gregorio Sirlin and Juan Queirel[8] (Hosp Tornu) report on 223 patients with combined pulmonary and extrapulmonary lesions The process began with the ex trapulmonary lesion in 47 99 per cent with the pul monary lesion in 39 45 per cent and with pulmonary and extrapulmonary lesions simultaneously in 12 55 per cent In 83 per cent of those with extrapulmonary onset, pul monary lesions were demonstrable roentgenologically, and in 58 4 per cent the pulmonary process was active and progressive Active pulmonary lesions tended to occur most frequently in patients with multiple extra thoracic foci, i e in those with tuberculous adenopathy, urogenital tuberculosis skeletal tuberculosis and cuta neous tuberculosis in the order named The tuberculous pulmonary lesions observed in this group of patients were in decreasing order fibrocaseous lesions chronic disseminated lesions with ulcerations and cavities infil trative lesions, fibrotic and cirrhotic tuberculosis, chronic disseminated tuberculosis without ulcerations and acute disseminated tuberculosis Most of the pulmonary lesions appeared roentgenographically to be of hematogenic ori gin, suggesting reinfection The incidence of active pul monary lesions was in direct relation to the age of the

(8) Sema a méd 49 45 64 July 9 194

patients up to 30 years then it showed a decrease The frequency of pulmonary tuberculosis was in inverse proportion to the duration of the extrapulmonary lesions up to a period of four years but it increased when the extrapulmonary tuberculosis dated farther back than four years this was attributed to pulmonary reinfection The course of the pulmonary and the extrapulmonary lesions ran independently from each other however in most cases the fate of the pulmonary lesion governed the prognosis of the tuberculous disease

Cases of tuberculosis with simultaneous pulmonary and extrapulmonary onset were particularly grave leading to death in more than 50 per cent of cases within a few months to three years The type of extrapulmonary involvement had a decisive influence on the prognosis the outlook with renal and multiple extrapulmonary foci being particularly grave Most of the pulmonary lesions in this group were of the hematogenic disseminated type

The most frequent types of extrapulmonary tuberculosis in cases of mixed tuberculosis with pulmonary onset were skeletal and urogenital lesions The most frequent forms of pulmonary tuberculosis which tended to become complicated by extrapulmonary lesions were the chronic disseminated forms with cavity formation the fibrocaseous form and the ulcerofibrous forms On the other hand patients with tuberculous pneumonic infiltrates rarely developed extrapulmonary lesions An antagonistic course of the pulmonary and extrapulmonary lesions was infrequent In only 9 per cent of cases was it observed that with arrest of the pulmonary lesion the extrapulmonary lesion progressed leading to cachexia amyloidosis and finally to death Conversely the much claimed beneficial effect of suppurating extrapulmonary tuberculous lesions on the progress of the pulmonary focus could not be observed in the present series except in few cases of anorectal involvement in which with the appearance of a suppurating fistula the pulmonary focus showed temporary improvement In general the prog

nosis in this group of cases is governed by the severity of the pulmonary lesion The appearance of the meta static extrapulmonary lesion indicates an aggravation of the pulmonary process manifested by progression of the pulmonary lesion and systemic repercussions

The mortality rate in this series of combined pul monary and extrapulmonary lesions was as follows in the group with extrapulmonary onset 26 42 per cent, in the group with simultaneous onset 53 56 per cent, and in that with pulmonary onset and metastatic foci 52 27 per cent *Progression of the pulmonary lesion was the* most frequent direct cause of death miliary tuberculosis and meningitis being next in frequency

Naturally Acquired Tuberculosis in Heterologic Hosts William H Feldman[9] (Mayo Clinic) states that natural occurrence of tuberculosis in most warm blooded mammals and fowls and in cold blooded ani mals such as alligators iguanas turtles frogs fish and snakes makes it evident that few if any species have an absolute resistance to the disease The natural host for the avian bacillus is the chicken However in addi tion to marked pathogenicity for other barnyard fowl and wild birds the avian bacillus affects swine sheep and occasionally cattle Man seems to have a high re sistance to the avian tubercle bacillus for there are probably less than 20 authentic human cases in the literature

The organism of bovine tuberculosis also may pro duce disease in swine dogs and cats Most birds are resistant although canaries and parrots may be af fected During the past decade several hundred cases of pulmonary tuberculosis in man due to bovine bacil lus were reported in England Scotland and Denmark although heretofore the intra abdominal tissues bones and joints were considered the usual sites for infection with this bacillus

The human type of tubercle bacillus is also capable

(9) Minn ot Med 26 437 439 May 1943

of producing serious tuberculous disease in heterol ogous hosts With the exception of the parrot birds are not susceptible to the human bacillus Swine may become infected Cattle rarely acquire naturally an infection with the human tubercle bacillus However cattle exposed to infective material from human beings affected with human tubercle bacilli may become suffi ciently sensitized to mammalian tuberculin to elicit a positive intracutaneous tuberculin reaction Therefore persons with active tuberculosis of the lungs should not be permitted to handle cattle because of the greater possibility of sensitizing the animal to tuberculin that may be used in subsequent diagnostic tests Dogs are susceptible to both bovine and human bacilli but are resistant to the avian type Cats are rarely affected by the human tubercle bacillus

Late Primary Tuberculous Infection —*Mode of De velopment* —W Loffler[1] states that it has recently been conceded that so called infiltrative tuberculosis of the adult is a manifestation of primary infection rather than a secondary or early infiltration Since the incidence of tuberculosis among the general population continues to be high even though the rapidity of its spread has diminished during the past decade it must be assumed that a great number of young adults be come infected for the first time This fact is of funda mental importance in regard to the epidemiology of the disease

The course of primary infection in adults is essen tially similar to that in children the prognosis is there fore not more unfavorable The clinical picture is not uniform In a great number of cases the infection runs a latent course while in a much smaller group it pro duces clinical manifestations In some cases only roent gen findings are present In others mild febrile states occur It is imperative therefore in the presence of obscure fever especially when there is no history of

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nosis in this group of cases is governed by the severity of the pulmonary lesion The appearance of the meta static extrapulmonary lesion indicates an aggravation of the pulmonary process manifested by progression of the pulmonary lesion and systemic repercussions

The mortality rate in this series of combined pul monary and extrapulmonary lesions was as follows in the group with extrapulmonary onset 26 42 per cent in the group with simultaneous onset, 53 56 per cent and in that with pulmonary onset and metastatic foci 52 2‹ per cent Progression of the pulmonary lesion was the most frequent direct cause of death miliary tuberculosis and meningitis being next in frequency

Naturally Acquired Tuberculosis in Heterologic Hosts William H Feldman[9] (Mayo Clinic) states that natural occurrence of tuberculosis in most warm blooded mammals and fowls and in cold blooded ani mals such as alligators iguanas turtles, frogs fish and snakes makes it evident that few if any species have an absolute resistance to the disease The natural host for the avian bacillus is the chicken However, in addi tion to marked pathogenicity for other barnyard fowl and wild birds the avian bacillus affects swine sheep and occasionally cattle Man seems to have a high re sistance to the avian tubercle bacillus for there are probably less than 20 authentic human cases in the literature

The organism of bovine tuberculosis also may pro duce disease in swine dogs and cats Most birds are resistant *although canaries and parrots may be af fected* During the past decade, several hundred cases of pulmonary tuberculosis in man due to bovine bacil lus were reported in England Scotland and Denmark although heretofore the intra abdominal tissues bones and joints were considered the usual sites for infection with this bacillus

The human type of tubercle bacillus is also capable

(9) Minne ota Med "6 437-439 M y 1943

is in order Likewise in groups in which tuberculous contacts have been detected tuberculin tests should be repeated after two to three months

Early Evolution—On the basis of autopsy material obtained from the Swiss Army E Uehlinger[2] found that 50 per cent of adults aged 20 55 have changes due to tuberculous infection The significance of late primary infection is attested by the fact that of 72

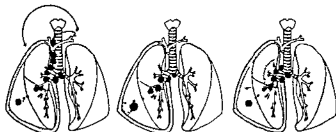


Fig 26—P thog f tub ul n pl t s—l te p im y nf ct n w th e ly pleu it *L ft* h m t gen u p ad t pleura c *nts* lymphog nou sp d of p m ry i fect n to pl *right* xt si n of pe ifoc l primary filt t n to pl

cases of miliary tuberculosis and meningitis observed in soldiers between 1939 and 1941 and proved at autopsy 60 originated from a primary complex The clinical manifestation of late primary infection is only exceptionally the expression of the primary infiltrate but is most commonly the sign of postprimary hematogenic or bronchiogenic spread The early postprimary manifestation may be erythema nodosum serofibrinous pleurisy tuberculous polyserositis Poncet s polyarthritis tuberculosis of multiple organs hematogenic pulmonary tuberculosis tuberculous meningitis or miliary tuberculosis

Erythema nodosum as a sign of early bacillemia or toxemia is rarely encountered in fatal cases of late primary infection in the Army or generally Tonsillitis pharyngitis and laryngitis are frequent early features

(2) S hw m d W h h 7 701 711 J 27 1942

previous tuberculous infection, to consider not only tuberculosis but a primary complex Two important criteria permit an unequivocal diagnosis of a primary complex (1) reversal of a negative to a positive tuberculin reaction and (2) transition of a soft bipolar roentgen shadow into a hard calcareous one The soft primary complex is rarely discovered In cases of generalized miliary tuberculosis and tuberculous meningitis in which the primary complex is proved at autopsy perihilar infiltration is often the only finding since the perifocal zone of the complex may be insignificant and atelectasis is frequently absent in adults

Erythema nodosum is a typical manifestation of the benign form of late primary infection More rarely, it may occur in protracted secondary stages of tuberculosis and very rarely during the tertiary stage Primary focus pleurisy is a frequent finding In the vicinity of each primary focus are lymph space tubercles so called resorption tubercles which usually extend into the adjacent free or interlobar pleura It is likely that the sharp chest pain complained of during the initial stages of primary infection is due to this epifocal dry pleurisy The exudative pleuritis of the young adult is frequently a sign of primary infection Primary focus phthisis in the adult is of great practical significance Its clinical course varies depending on whether resorption induration or a breaking down of the focus with bronchiogenic spread occurs Its further course does not differ from that of tertiary phthisis Primary infection of the digestive tract (tonsils lower small intestine) is rare, but does occur

Primary infection in adults is of exogenous origin The environment must therefore be thoroughly investigated as to contacts In the army, officers as well as privates should be included in the investigation In view of the frequently prolonged latent period between entrance of bacilli and appearance of the roentgen picture of the primary complex repeated mass roentgenography

cases of adult phthisis are the result of late primary infection rather than of childhood tuberculosis

There are certain morphologic differences between the postprimary stage of the adult primary complex and that of childhood tuberculosis (1) The hematogenic metastases in patients under 18 are usually located in the meninges while in patients over 18 they appear in the lungs serous membranes and genital organs (2) Phthisic evolution is an exception in childhood but the rule in adult age The morbidity of late primary infection is greater than that of childhood tuberculosis because of the age linked disposition toward generalization in adolescents The circumstances which lead to malignant development of late primary infection are not known but certain known symptoms indicate an unfavorable prognosis These are continued high sedimentation rate leukopenia with progressive appearance of immature forms myoblastic reaction persistent tachycardia loss of weight spiked fever curves and failure of primary pneumonia to resolve during the first half year

Clinical Data—St J Leitner[3] reports on 48 cases Most of the patients had subjective symptoms Thirty seven complained of fatigue 16 of cough and 2 of expectoration Fever was present in 33 The right lower lobe was most frequently involved In only five cases was the erythrocyte sedimentation rate normal in the remaining cases it was increased in some markedly so Immature white blood cells were noted in 28 cases monocytosis in 12 and blood eosinophilia in 9 Sensitivity to tuberculin was pronounced in all erythema nodosum was present in one third The frequency of erythema nodosum the high sensitivity to tuberculin and tissue eosinophilia found in a biopsy specimen removed from an erythematous nodule suggest early allergy Tuberculous contact was proved in 28 cases The course of primary infection was uncomplicated in 29 In 11 there

3) Sh m i W h h 7 11 71 J 7 194

of hematogenic tuberculosis In almost every case of late primary infection pleurisy develops The pathogenesis of this pleural involvement is shown in Figure 26 It is frequently a precursor of further hematogenic spread The simplest type of early hematogenic dissemination following primary infection in adults is *tuberculous meningitis* *It is heralded by two fever* episodes one during the transformation of the primary caseous pneumonia into a primary infiltrate and another during the hematogenic dissemination and metastasis to the meninges The commonest type of early hematogenic dissemination is the progressive protracted type with terminal miliary tuberculosis Dissemination into the kidneys adrenals prostate osseous system and central nervous system may be asymptomatic for some time except for fever episodes Striking is the unilateral metastasis into the pleura prostate seminal vesicles and epididymis which is probably due to constitutional predisposition as no anatomic basis had been found

More frequent than the early hematogenic spread is the canalicular dissemination of the late primary infection A small degree of dissemination due to the breaking down of the primary pneumonic focus is common and may be detected clinically by the temporary positive sputum It usually leads to a *perifocal* spread and may through swallowing of the bacilli containing sputum result in ileocecal tuberculosis with caseation of regional mesenteric nodes The breaking through of tracheobronchial lymph nodes into the bronchi adjacent to the hilus produces aspiration pneumonia in the area of primary infection Cavity formation in the primary complex and breaking through of caseous lymph nodes into the trachea and bronchi give rise to primary phthisis The numerous cases of progressive tuberculosis with pronounced caseation of tracheobronchial lymph nodes encountered in post mortem examination on soldiers indicate that many

susceptible person should be exempt from military service and the soldier discovered to have primary infection should receive thorough and prolonged treatment

[Massive tuberculous hilar adenitis is not necessarily a criterion of primary infection —Ed]

The Round Pulmonary Tuberculous Focus I D Bobrowitz[5] (Otisville N Y) reports on 55 patients with round pulmonary foci 30 of whom were males



Fg 7—L dot v w Ap 1 194 1 g bul te 1 p al und fo O dm D 11 1941 y l g p 1 th k w ll d cul of filt t w th t l rr g l f l ing app tl ca t p tum g t L ft p m th t rted D 15 1941 C t f med h m g u ly h rply d fi d d f j b th p s w th p rt l l ft p m th d p t l u d t t n n ght d

and 25 females 47 white and 8 colored Most patients were between 20 and 40 Only 1? per cent of the round lesions were in the apex the others were in the infraclavicular area and above the level of the second anterior interspace The lesions were classified in two groups

1 Found Completely Formed On first examination this was noted in 33 cases The focus was circular well defined and homogeneously dense In 4 of these there was evidence suggesting that the round focus was preceded by a cavity It was found on subsequent ex

(5) Am R v T be 4 4 483 M 1949

was pleurisy with effusion in 2, polyserositis, in 4, intrapulmonic progression in 1, tuberculosis of the elbow joint, and in 1 generalized caseating tuberculous adenopathy There was one case of extrapulmonary primary complex in the conjunctiva and one in the tonsil The mortality rate in this series was 4 per cent It should be borne in mind however that the patients were treated in the sanatorium for an average of only six months

[Exception must be taken to the statement that "infiltrative tuberculosis" of the adult is a manifestation of primary infection since our experience indicates that this is not a dependable criterion. The important point to emphasize is that every newly developed case of tuberculosis should be treated promptly on its detection —Ed]

Notes on Primary Pulmonary Tuberculosis in the Army Maurice Gilbert[4] (Geneva) states that the war has thrown a new light on the problem of tuberculosis in the army Statistics published by the various armies notably in Norway and France indicate that 30-35 per cent of anergic young soldiers become positive tuberculin reactors or acquire primary infection while in service In Switzerland 5 per cent of soldiers have acquired primary infection since mobilization in 1939 This figure does not include cases of pleurisy with effusion which might well have resulted from a recent primary infection It is felt that the percentage is much higher for primary tuberculous infection may pass unnoticed clinically or may be disguised as a banal type of infection Of all criteria of primary pulmonary infection Gilbert considers the roentgenogram as the most reliable for massive hilar adenitis in an adult is pathognomonic for primary infection since only a hitherto anergic individual can produce such reaction

Case finding in the army should be done with great thoroughness and preferably in collaboration with a civilian organization engaged in tuberculosis control Every individual with active tuberculosis and even a

(4) Radiol el 11 79 85 March 1942

round foci are the end result of tuberculous cavitations

Eighty two per cent of the lesions were unchanged during observation or became smaller However 9 per cent of patients had cavitation and 2 of these progressive tuberculous lesions At last examination another 9 per cent had marked enlargement of the focus Such cases require collapse therapy

[Round infiltrate may appear an evolut on of lesions wh ch apparently we e neve excavated these represent encapsulated cas ou collect ons —E1]

Early Diagnosis of Pulmonary Tuberculosis is stressed by R P Trail[6] Among the undoubted warnings in past and present histories of tuberculous patients which many doctors either ignore or fail to investigate are hemoptysis pleurisy cough of more than a month s duration persistent indigestion nausea or actual sickness with meals especially breakfast an unnatural lassitude often accompanied by face flushes in the afternoon fistula in ano amenorrhea and erythema nodosum Long before added sounds in the chest appear the usual initial silent area of bronchopneumonia presents two definite physical signs lack of movement of the base of the affected side and evidence of mediastinal shift While the stethoscopic signs of fibrosis and the x ray findings of tracheal and mediastinal shift are still absent the patient with a unilateral and early lesion shows a diagnostic tension of the origin of the sternocleidomastoid at the inner end of the clavicle on the same side When added sound appear they are slight at first and are found only in the early hours of the day before mucus is coughed up These sounds have characteristics which differentiate them from the sounds of simple bronchitis They are unilateral are seldom found at the base and are made more insistent with the depth of inspiration whereas in simple bronchitis they are most evident in the first half of inspiration

Estimation of the sedimentation rate of erythrocytes

(6) I t 413 416 O t 10 194

amination in eight cases In subgroup 1 (three patients) the round focus was found completely formed years after the first film, which did not show such lesions was taken and in an area of lung previously clear In subgroup 2 (five patients) the round focus was found on subsequent examination in an area of lung that was the site of tuberculous involvement

2 Formation Observed Seven patients showed a round focus after spontaneous closure of a pulmonary cavity In one of them with bilateral cavities (Fig 21) closure occurred on one side spontaneously and on the other with pneumothorax The cavity walls, which were usually thick became heavier, the central area of translucency filled and a circumscribed dense homogeneous area resulted in an average of about five months *Eight other patients had round foci formed by* closure of cavity by pneumothorax Transformation of the cavity into a round focus occurred in half the cases within one month in three in less than 2 months and in one after partial absorption of the pneumothorax

None of the patients presented the typical picture of primary infection of the lungs Moreover some had old hilar calcifications and many had additional parenchymal lesions In 85 per cent the round lesion was single and most had no, or scant, surrounding or additional infiltration In no patient was there evidence of bilateral symmetrical hematogenic pulmonary dissemination Nor were there any extrapulmonary lesions which *would indicate a hematogenic source* These findings indicate that the round foci are reinfections and usually of bronchiogenic origin The most important fact is that every case in this series that could be followed from the beginning through all phases of production to the final appearance of the round focus showed transformation of a tuberculous cavity into this special type of lesion In most patients conversion of sputum from positive to negative occurred after formation of the round focus *Bobrowitz has come to the conclusion that the*

groups of most heavy morbidity and mortality would be covered Initial cost would shortly be offset by the saving of vast sums of money now spent on hospital treatment in advanced cases

[Our experience indicates that most early pulmonary lesions are exudative and l able to necros s and excavation —Ed]

Some Problems in Connection with Early X Ray Changes in Adult Pulmonary Tuberculosis are discussed by G Simon[7] (St Bartholomew s Hosp London) In the early stages of pulmonary tuberculosis there may be no symptoms Increased use of mass surveys is revealing more early cases radiologically Some at first are without convincing clinical bacteriologic or serologic evidence of disease only later events prove the lesions are tuberculous Simon emphasizes that this adds to the responsibility of the radiologist who should



F 28—R u d f

(7) B it J R d l 16 17 19 J ly 1943

may aid in early diagnosis A fall below 10 per cent with the micromethod or 8 with the Westergren method is suggestive and should be considered in the summation of a doubtful case The patient with active disease will often fail to have a pulse rate below 90 in 5 minutes or a normal rectal temperature of 99 F in half an hour after a brisk walk for 20 minutes

On x ray examination lagging of the diaphragm and loss of translucency on the affected side are early findings in screening On the film the first variation from normal lung shadows takes one of two main forms in the early stages of the disease proliferative and fibrocaseous or acute and exudative The former is by far the more common in young adult tuberculosis and usually presents a rounded area of loss of translucency in the inner or outer third of the subclavicular region on one side of the chest This is known as 'Assmann's focus In many cases however the focus has broken down to cavity formation by the time of its discovery Experience with mass roentgenography shows that there is a type of proliferative upper zone disease that is much more common than formerly believed—true apical tuberculosis Acute nonfibrous exudative phthisis is a much rarer finding Its x ray shadows are not unlike those of bronchopneumonia They differ from the latter in that the edges of the shadows are more woolly and the shadows are smaller and more numerous with a tendency to be confined to or more marked in, the upper and mid zones of the lung fields They are the evidence of inflammatory exudate filling the acini and caseating and disintegrating freely, as it is uncontrolled by the fibrous tissue and the giant cells of the proliferative form of the disease

Immediate hopes for future control and treatment of pulmonary tuberculosis must be based on periodic mass roentgenography of the adolescent population If surveys are begun at school leaving age and are followed by annual review up to the age of 30 the age

groups of most heavy morbidity and mortality would be covered Initial cost would shortly be offset by the saving of vast sums of money now spent on hospital treatment in advanced cases

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Fig 28 —Round f

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(7) Brit J Rad 1 16 17 19 July 1943

be able to give some help on the probabilities of prognosis Additional study and reports on the outcomes of mass surveys are needed to evaluate the true significance of small radiologic shadows in the lungs

Two types of lesions are seen the round focus about 1 cm in diameter or a small smudge of opacity not



F 9 —Smudge focus

much larger but not so well defined or circular in shape in the subclavicular area a group of low density mottled opacities 1 3 mm in size below the clavicles or in the midzone Simon believes this grouping should not be too rigid because in one of his cases an area of mottling resolved and later a round focus appeared while in two others an isolated round focus was later surrounded by mottled shadows Figure 28 shows a round focus in a woman 23 found in a mass survey The sedimentation rate was 4 and the sputum nega

tive After a short period of observation in a sanatorium she was discharged with good prognosis Another patient of similar age and build, whose roentgenogram showed a similar round focus was observed for nearly a year without any further changes after which additional opacities appeared nearby Figure 29 shows a smudge focus in a girl 18 who was a contact The



F g 30 —S me ase pr d g f u m ths l t

only sign or symptom was a slightly raised sedimentation rate She was sent to a sanatorium and despite rest in bed the lesion excavitated and then tubercle bacilli were found in the sputum Figure 30 shows the appearance four months after the lesion was discovered

These cases illustrate some of the difficulties associated with these lesions In the absence of any history of colds or pneumonia they are unlikely to be due to areas of nontuberculous pneumonitis Many of the

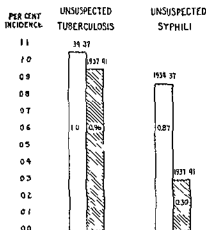
opacities in Simon's series remained stationary or slowly resolved, in these there is no proof that they were tuberculous, but there is also no proof of any other etiology The lesions that progressed were eventually proved tuberculous His impression is that th round focus is tolerably benign, if there is no abnormality clinically and that a third of the smudge foci will progress and rather more of the mottled foci He believes that serial observations should be adequate and that these should not be abandoned if the lesion remains stationary for a month or so

Problem of Unsuspected Tuberculosis in Pregnancy Incidence by Roentgenologic Technic Compared with Incidence of Unsuspected Syphilis C Wesley Eisele William B Tucker Robert W Vines and John L Batty[8] (Univ of Chicago) point out the inadequacy of symptoms and physical examinations as means of diagnosing pulmonary tuberculosis An error of 90 per cent may be expected when these methods alone are used Routine chest fluoroscopy, followed by roentgen study in all cases of definite or suspected lung pathology is a satisfactory method of finding tuberculosis when carried out by an experienced examiner trained in fluoroscopic technic and lung pathology

Application of this method to 10 968 pregnant women unselected except for exclusion of known tuberculosis disclosed 110 cases (1 per cent) of unsuspected clinically important tuberculosis Seventy four cases were shown to be active during pregnancy Incidence of unsuspected tuberculosis remained nearly the same for the two periods of this investigation namely, 1 06 per cent during 1934 1937 and 0 96 per cent during 1937 1941 In contrast to this incidence of unsuspected syphilis declined markedly, from 0 87 per cent during 1934 1937 to 0 30 per cent during 1937 1941 This may be attributed to passage of the Illinois hygienic marriage law in 1937

(8) Am J Ob t & Gy e 44 183 195 Augu t 194

Routine chest roentgen examinations should rank with routine Wassermann tests as a medical necessity in pregnant women Tuberculosis in pregnant women is still an important problem for although it has declined from first to seventh place as a cause of death in the general population it remains the leading cause of



F g 31—C mp i n f inc den of u u p ted tub ulosi d u p t d yph l s n p egna t w m n tw p od 1934 1937 a d 1937 1941 S ght d lin i tube ul nt t w th m k d d l f yph l ft p g of Illin hyg marr ge l w in 1937

death of women of child bearing age The tuberculosis toll in this age sex group accounts for 20 per cent of all deaths twice as high a mortality as from all puerperal causes

Demonstration of Tubercle Bacilli in Minimal Pulmonary Tuberculosis W P Decker W H Ordway and E M Medlar[9] (Mount McGregor N Y) report that repeated examinations of sputum and fasting gastric contents by culture and guinea pig inoculation disclosed tubercle bacilli in 67 of 97 patients with clinically active minimal pulmonary tuberculosis over a

(9) Am Re Tub 47 625 630 J 1943

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(8) Am J Obst. & Gyn c 44 183 195 August, 1942

lacking or disappear when it is high leaving only granular forms Especially in old fibroid lesions that are healing granules alone may be found If nodular and infiltrative lesions ulcerate many of them develop acid fast bacilli on the exposed surfaces Variation in age and race and various diseases such as diabetes and silicosis seem to cause a variation in the number of acid fast bacilli found Colored races and certain blond white races are prone to have more bacilli in their sputum than others Diabetics tend to have an increase in bacilli Silicosis is noted for scarcity of bacilli in the sputum However when a tuberculous patient reaches an equilibrium with his disease the number of bacilli remains remarkably constant

In approximately a five year period the following findings as regards tubercle bacilli were obtained on patients admitted to the Municipal Sanatorium

	%
Positive on direct smear	00
Negative on direct smear positive on concentration	13 09
Negative on concentration positive on culture and animal inoculation	[illegible]
Negative by any other method positive on stomach lavage	[illegible]
Entirely negative	4 16
Nontuberculous	79
Total	100 00

These figures reveal that even the best direct smear will fail to demonstrate tubercle bacilli in 25 21 per cent of cases With all other methods there are only 4 16 per cent in which bacilli are not found For an all purpose method the Ziehl Neelsen procedure still heads the list For best results the smear should be counterstained with a 10 per cent aqueous solution of Loeffler s methylene blue rather than the pure solution because the heavy blue conceals many weakly stained bacilli Excellent results have been reported recently with Spengler s picric acid counterstain for thick smears and tissue sections The recent fluorescent microscopic method of Hagemann deserves mention Of

period of five years In a previous five year period when the more thorough laboratory methods were not in routine use tubercle bacilli were demonstrated in only 24 of 172 cases Gastric lavage studies gave positive results in 41 of 56 'no sputum" cases Sputum smears were positive in but 16 of 269 cases This is no true indication of the number of patients who were discharging tubercle bacilli A high percentage of patients with clinically active minimal tuberculosis discharge tubercle bacilli to a greater or lesser degree It is difficult to determine when patients with minimal disease are entirely free from bacilli and to evaluate the significance of an occasional discharge of a few bacilli

The Underlying Principles and Minimum Standards of Laboratory Examination for Tubercle Bacilli are pointed out by Henry C Sweany[1] (Chicago Munc Tuberculosis Sanatorium) The causative organism of tuberculosis is not always a bacillus and is not always acid fast It may be overlooked if only a superficial examination is performed Furthermore in about one fourth of cases no bacilli can be found except by most exacting methods Most significant from the diagnostic standpoint are forms that only simulate tubercle bacilli such as nontuberculous acid fast smegma, butter and timothy bacilli acid fast spores acid fast inclusions in cells particularly yeast cells nonacid fast bacilli accidentally covered by paraffin small cracks in glass slides etc One of the most common technical errors is the use of blotters to dry slides or of coplin jars to stain them where bacilli may be transferred from a positive to a negative slide use of unclean glassware failure to wipe off the lens failure to decolorize the slide sufficiently and finally spontaneous infection in guinea pigs which have previously been exposed to infection

Acid fast bacilli seem to increase when resistance is

(1) Am J Clin Path 1 458 466 S pt mber 194

in the human cases from which strains are isolated and pathogenicity Moreover tuberculin and coccidioidin for the respective skin tests while specific for each do not exhibit 'strain differences

The principal portal of entry of the two organisms is alike the respiratory tract Subsequent localization pneumonitis development of allergy and focalization of the primary infection are also similar In both conditions the result may be a walled off lesion which may calcify The erythema nodosum of primary coccidioidomycosis like that associated with primary tuberculosis occurs soon after allergy is first established when the patient is hypersensitive It may possibly be a reaction of these very sensitive tissues to circulating antigen Postprimary erythema nodosum due to either infection is rare

The pathogenesis of coccidioidal granuloma seems to be that of an endogenous reinfection Primary infection of Coccidioides immitis not only does not predispose to the granuloma but actually confers a lasting immunity to exogenous infection As in tuberculosis the ability to focalize a coccidioidal infection seems to depend on some unknown quality of the host

Prognosis and Treatment

Prognosis in White and Colored Tuberculous Children According to Initial Chest X Ray Findings Miriam E Brailey[3] (City Health Dept Baltimore) reports that among 404 white and 744 colored children under 15 when found to give a positive reaction to tuberculin chest lesions demonstrable at initial x ray examination were more frequent and more serious in extent the younger the child Infected children under 1 year behaved with remarkable similarity irrespective of race showing enlarged tracheobronchial lymph nodes in about 22 per cent and extensive lesions of the lung parenchyma in 47 per cent For white children prompt

(3) Am J Pub H 33 343 352 Ap 1 1943

the concentration methods, the sodium hydroxide method in which the total exposure does not exceed 45 minutes is perhaps the best. With ordinary sputum total exposures of 30 minutes are adequate. With feces and urine specimens the exposure must be 45 minutes especially in the presence of spores and spore forming bacilli. A period of incubation of 15 hours preceding the sodium hydroxide treatment helps to autolyze and destroy more cellular debris but is objectionable to some because of offensive odors developing.

Safety trays containing 36 bottles wherein the bottles may be stoppered and locked in by a lid pressed down on the corks are useful for transporting raw specimens. A convenient apparatus for handling a large number of specimens is a three heat electric staining bath and slide tray made in 20 and 6 slide size. The rack has metal posts and barricades so that the slides cannot fall off. These trays permit proper drying, fixing and staining with no chance of error.

For culturing, Saenz medium is superior to all others and is the simplest to make. Next in efficiency is the Loewenstein medium, as modified by Jensen and Holmes. For growing bovine bacilli the material must be first inoculated into guinea pigs or on medium without glycerin.

A last step in testing for tubercle bacilli is lavage of the stomach with direct examination, culture and inoculation of the sediment into animals. The detailed outlines for finding tubercle bacilli given by the Minimum Laboratory Standards Committee of the American Trudeau Society are recommended to all clinical and health department laboratories.

Parallelism of Coccidioidal and Tuberculous Infections. According to Charles Edward Smith[2] (Stanford Univ.) Mycobacterium tuberculosis and Coccidioides immitis have several things in common. There is no correlation between the severity of the clinical pictures

(2) Radiology 38 643-648 June 194

findings on first x ray examination between 3 and 15 had no mortality during the period of observation while colored children between these ages whose initial films showed no parenchymal lesions had a mortality of 3 3 per cent during the 10 year period The lower death rate in children past infancy appears to be related to lessened frequency of parenchymal involvement and to an improved resistance to nodal lesions

[In children and young adults proper treatment improves materially the prognosis of the disease Unfortunately some hold the fatalistic view that treatment makes no difference The following article speaks to the contrary —Ed]

Tuberculosis in Adolescents and Young Adults is discussed by Ralph Horton[4] (Homer Folks Tuberculosis Hosp Oneonta N Y) The records on the first 100 white patients aged 15 24 who underwent treatment for the first time and remained in the hospital 90 days or longer were studied with particular reference to the influence of treatment on the behavior and ultimate outcome of pulmonary tuberculosis in adolescents and young adults There were 32 males and 68 females Thirty nine were aged 15 19 and 61 aged 20 24 The longest period of treatment was six years and the shortest three months the average length of stay being one year and two months Seventy three had symptoms which suggested the examination leading to diagnosis which was based on roentgen evidence in 83 cases on sputum examination in only 13 and on physical findings in 4 On admission the cases were classified as minimal 35 moderately advanced 29 and far advanced 36 The disease was unilateral in 35 and bilateral in 65 In a little more than half the cases the disease was of the predominantly exudative type In 63 there was x ray evidence of cavity Tubercle bacilli were found in the sputum or by culture of gastric washings in 89 of the cases

Seventy two patients were discharged with the disease arrested or apparently arrested and 20 with it

(4) N w Y k St te J M 4 131 213 N 1 194

reduction in frequency of parenchymal lesions was noted as early as 1 year but colored children showed a sustained high prevalence of such lesions on initial examination for the first three years of life and barely approximated the decreasing risk noted in year old white infants by the time they had reached 5 years

Among children aged 5 15 on first examination roughly 30 per cent of infected children of both races showed nodal involvement For the white, parenchymal lesions of any kind were rare occurring in less than 2 per cent For the colored parenchymal involvement of the childhood type appeared in nearly 6 per cent of initial films and lesions of reinfection tuberculosis were seen in over 1 per cent at first examination

In a 10 year period of observation, mortality from tuberculosis in white children infected before age 3 was calculated to be 8 per cent while for colored children it was nearly 20 per cent For both races more than half the risk of death was concentrated within the first year of known infection When infection was discovered between 5 and 15 years, the 10 year mortality for whites was 0 4 per cent and for colored 7 6 per cent Mortality was much higher for children admitted with parenchymal lesions For the combined races if infection occurred before age 3 mortality was 21 per cent within 1 year had risen to 30 per cent by the end of 5 years and to 32 per cent for the whole 10 year period The risk of death is about equal in white and colored children if parenchymal disease is present The colored show many more of these serious lesions than do white children Lesions of the lung parenchyma on first x ray in older children of the colored race carried the same mortality as in younger children, but at these ages they were less frequent

The total 10 year mortality from tuberculosis in white children infected before the age of 3 and showing only nodal lesions or negative films was 4 per cent and in colored 7 6 per cent White children with similar

coefficient based on experiments with pure liquids connected v with the time of flow The normal value of $100v$ is of the order of 1 5 cm per sec or 1 5 poises per Gm per cc

The degree of correlation between viscometric and clinical gradings was studied in 53 cases of tuberculosis In 10 of these viscosity measurements were repeated with the object of comparing individual viscosity and clinical changes In the 53 single tests agreement between clinical observations and viscosity measurements was between 87 and 92 per cent In the double tests the most outstanding change recorded was a fall in viscosity of nearly 10 per cent in 14 days coinciding with the beginning of closed suction drainage and well marked improvement in the patient's condition In these 10 cases all changes in viscosity of 2 5 per cent or more were accompanied by patent changes in condition It is concluded that measurement of plasma viscosity gives a good indication of the severity of pulmonary tuberculosis

Treatment of Tuberculosis with a Low Carbohydrate Diet is reported by Benjamin P Sandler and Rudolph Berke[6] (Montefiore Hosp New York City) Ten patients with advanced pulmonary tuberculosis were treated with such a diet on the assumption that it would increase oxidations in the entire organism by removing the depressant effect of carbohydrate rich foods on bodily oxygen consumption Continued ingestion of a diet containing carbohydrate rich foods may depress glucose oxygen consumption by producing hypoglycemia in nondiabetics and by aggravating an already existing disturbance in carbohydrate metabolism in patients with a tendency to hyperglycemia In tuberculous patients who show neither hyper nor hypoglycemia the organism consumes more glucose and oxygen on a carbohydrate poor diet probably because such a diet makes available a more reactive form of

(6) Am R Tub 46 3 61 S pt mb 1942

quiescent or active there were 8 deaths Bed rest was effective in the cases of minimal involvement, in that in 25 of the 35 cases in this group the disease was controlled in this manner Of the 63 cases with cavity spontaneous closure was effected in 23 per cent by bed rest Collapse therapy was used in only 5 of the minimal, 17 of the moderately advanced and 25 of the far advanced cases The percentage of arrest was the same for bed rest as for collapse That the prospect for recovery depends largely on the extent of the tuberculous lesion is shown by the fact that in 30 of the 35 minimal cases the disease was brought into control, at least temporarily, while this occurred in 22 of the 29 moderately advanced cases and in only 20 of the 36 far advanced cases The outlook in the 15 to 19 year age group seemed to be slightly less favorable than in the older group and the percentage of deaths was higher in the younger group

Sixty seven cases were followed for 1 year or more the average being 2 years and 10 months At the end of the follow up period the percentage of those arrested was approximately the same as at the time of discharge

Plasma Viscosity in Pulmonary Tuberculosis Experiments by A K Miller and R B Whittington[5] have shown that in sedimentation tests with controlled cell volumes at constant temperatures the maximal velocity is largely dependent on the agglutination power of plasma and that this power can be demonstrated as a complex function of plasma viscosity It therefore seemed possible that plasma viscosity might serve as a useful clinical index

This report covers 76 viscosity measurements 63 of which were made on tuberculous patients The kinematic viscosity coefficient (v = absolute viscosity divided by density) of the citrated plasma was measured at 20 C in a modified Ostwald viscometer A varying

(5) L n et 2 510 511 O t 31 194

Shields[7] (Northville Mich) studied 40 unselected consecutive cases in which bronchial tuberculosis was demonstrated by bronchoscopic examination and pneumothorax was used to control the parenchymal disease Only cases with definite ulceration or stenosis were included Of the 40 patients 17 are dead (42 5 per cent) Three are still hospitalized with uncontrolled disease and 20 have been discharged with quiescent or apparently arrested cases Of the latter 9 have unexpandable lung and 14 had a bronchial disease which was of limited extent or responded to local treatment Only six of the discharged group had stenosis or extensive ulceration which had not shown tendency to regression Atelectasis usually lobar in extent was noted immediately or shortly after induction of pneumothorax in 43 per cent and in most of these re expansion was impossible even if attempted early In 17 5 per cent anaerobic infection of the atelectatic lung was observed Tuberculous empyema occurred in 43 per cent In 12 patients atelectasis and empyema coexisted and 11 of these died In nearly all other fatal cases the downhill course could b linked with induction of pneumothorax The fatality rate in the 6 minimal cases was 83 per cent 13 of the 17 empyema patients died only of whom had far advanced pulmonary disease and of 17 with atelectasis 12 died only 3 of whom had advanced pulmonary disease This indicates that the fatality rate did not follow in direct ratio the stage of pulmonary di ease On the other hand 54 per cent with stenotic lesions of the bronchi 50 per cent with extensive ulcerations and only 27 per cent with mild or moderate ulcerations died

The following plan of management is suggested therefore in cases of pulmonary tuberculosis complicated by bronchial tuberculosis The diagnosis having been made primary attention is paid to the type of bronchial lesion and the idea of collapse therapy is

(7) J Th S g 1 5 33 F b 1943

glucose γ glucose It is also likely that a low carbo hydrate high protein diet can bring about a normal liver glycogen storage Susceptibility to, and persist ence of tuberculous infection are likely fundamentally related to the amount of glycogen stored in the liver For this reason good nutrition and physical and men tal rest have been effective in treatment of tubercu losis Rest is effective because it makes available for healing processes glucose and oxygen which might have been used for muscular energy

The diet in the present series of cases ranged from 2 309 to 2 920 calories (carbohydrate, 114 124 Gm protein 101 129 Gm fat 161 212 Gm) This was di vided into three regular meals with feeding between meals and at bedtime of a milk and cream mixture Six thin soda crackers were allowed each day except for the soda crackers the carbohydrate content of the diet was ingested in the form of 5 and 10 per cent vege tables and fruits and dairy products

All 10 patients responded to the diet by gain in strength general clinical improvement and clearing of cavities and of infiltrations Seven gained 5 25 lb Patients who lost weight did so during the first few weeks thereafter the weight became stabilized or showed a rise Relief from precordial pain heaviness over the chest, palpitation and dyspnea was also ob tained in all patients after a varying period The cardiac symptoms apparently arise from partial depriva tion of the heart muscle of glucose Respiratory symp toms were either completely relieved or greatly ameli orated The sputum decreased gradually in amount and became more watery Striking was also the improve ment in the mental and emotional states Of the 10 patients 5 returned to home 2 were made ready for surgery and 3 are still at the hospital and continue to improve

Management of Pulmonary Tuberculosis Complicated by Bronchial Tuberculosis F N Rafferty and D O

ing lymph nodes Upper (or lower) lobectomy is carried out by individual ligation technic Following upper lobe resection the lower lobe if adherent is mobilized so that it may ascend to fill the apex Intrathoracic crushing of the phrenic nerve has been done to reduce temporarily the volume of the hemithorax but the advisability or necessity of this remains to be proved

Silk technic is used throughout except for a proximal row of sutures penetrating the bronchial mucosa, where fine chromic catgut is used The pleural cavity is closed without drainage and the chest wall muscles approximated by interrupted sutures of fine silk Intrapleural pressure is adjusted to a moderate degree of negative pressure An oxygen tent is used routinely for the first 24 hours after operation Fluid or residual air may be reduced with needle aspiration according to individual indications, preferably maintaining a moderate degree of negative pressure

If lobectomy has been planned technical difficulties that lead to resection of the entire lung must not be countenanced The goal of the operation is conservation of normal lung tissue as well as ablation of the disease focus Interlobar fissures that have been obliterated by adhesions or anatomically incomplete fissures can and must be developed by careful dissection Discovery of healed foci in adjacent lobes is not an indication for resecting them

The authors conclude that lobectomy provides a more selective and immediate method of eradicating certain lesions of tuberculosis than does collapse therapy It may be used subsequent to artificial pneumothorax When bed rest alone is insufficient to bring the disease under control pneumothorax or phrenic nerve paralysis may be added If there is good reason to believe that the therapeutic goal of a re expanded lung with a closed lesion cannot be achieved within a reasonable time lobectomy may be considered when the acute phase has been brought under control

Lobectomy which combines conservation of lung function with immediate conversion of the sputum and a shortening of the span of treatment cannot be dismissed until its scope has been more fully explored

abandoned temporarily A longer than average trial of bed rest is given, during which time the efficiency of raising sputum is increased and bronchoscopy is used to treat the ulceration and to aspirate secretions If the parenchymal disease remains a threat to life, it must now be controlled The choice of procedures de pends entirely on the character of the bronchial lesion Pneumothorax may be used safely only when the bronchial disease is minimal or, if moderately exten sive, responds readily to local treatment, it is particu larly dangerous in cases with retained secretions Thoracoplasty under such conditions has at least three advantages over pneumothorax (1) atelectasis and its serious sequelae as a result of bronchial occlusion are infrequent (2) there is no infected pleural space, (3) relatively complete and permanent collapse may pre vent occurrence of late suppurative changes in the lung

Lobectomy for Pulmonary Tuberculosis is discussed by Edward D Churchill and Robert Klopstock[8] (Har vard Univ) with a report of six cases Three patients *provided orthodox indications for resection* of the lesion by lobectomy the other three presented the usual indications for thoracoplasty but lobectomy was performed by election Healing per primam occurred in all

TECHNIC —All patients should be subjected to bronchoscopy preoperatively to rule out active ulceration in the trachea or stem bronchus Gas oxygen ether anesthesia is administered through an intratracheal tube The incision is posterolateral with resection of a single rib at the appropriate level In areas overlying densely adherent cavities dissection is transferred from the intrapleural to the extrapleural plane In seeking a fissure, however, return to the intrapleural plane is necessary Meticulous hemostasis is maintained by ligatures and silver clips The frequently repeated statement that access to the hilus may be blocked by tuberculous infiltration of lymph nodes is erroneous Once the primary lesion is established, tubercu lous foci in an organ do not produce a lesion in the correspond

(8) Ann Surg 117 641 659 M y 1943

the Montefiore Country Sanatorium and admitted to the Altro Work Shops a medically controlled garment factory for a rehabilitation course between 1915 and 1939 and followed to the closing date of the survey July 1941 The longest period of follow up was 25 years the shortest 1½ years Ninety seven per cent of the patients were traced 5 years and 92 per cent 10 years In the earlier period 1915 1929 only 6 per cent of the patients received collapse therapy before admission to the Altro Shops in the later period 1930 1939 52 per cent received collapse therapy Four of every five patients had moderately advanced and far advanced lesions on entry to the workshop In 64 per cent of the cases the lesions were arrested and in 8 per cent they were unstable or frankly active The latter group dates back to the 1915 1929 period Thirty per cent of patients had no record of a positive sputum before admission to the workshop 55 per cent had a positive sputum which had been successfully converted to negative before admission and 15 per cent still had positive sputum on admission The percentage of patients with successful sputum conversion before admission to the workshop rose from 38 per cent in the 1915 1929 period to 69 per cent in the 1930 1939 period The percentage admitted to the workshop with positive sputum fell from 25 per cent in the 1915 1929 period to 6 per cent in the 1930 1939 period The median stay of the patients at the workshop was 16 8 months

At the end of 10 years after discharge from the Altro Shops 87 per cent of the patients with minimal lesions 86 per cent of those with moderately advanced lesions and 63 per cent of those with far advanced lesions had survived Of patients with successful sputum conversion before admission to the workshops and patients who had no record of positive sputum 84 per cent were alive at the end of 10 years only 54 per cent of those admitted with positive sputum survived

Clinical Management of Intestinal Tuberculosis This study by William M Peck and Julia M Jones[9] (Maybury Sanatorium Northville Mich) was undertaken to evaluate the effect of vitamin C on intestinal tuberculosis This was done by maintaining vitamin C saturation in a test group of patients known to have tuberculous enteritis and by permitting a similar control group to continue unsaturated Both groups were placed on a high calorie high carbohydrate diet made up of bland low residue foods served in five portions After finding a base line for each patient over a period of three days a test dose of ascorbic acid was given each patient in the test group in varying dosage until saturation was obtained From 1 to 2 Gm was required Saturation was then maintained by continued administration of a daily dose determined by urinary output This amount varied from 50 to 300 mg All patients had moderately or far advanced pulmonary tuberculosis

Fourteen patients were saturated with vitamin C for nine months In six of these there was excellent control of all intestinal symptoms in six definite improvement in two no response Of eight patients maintained on a similar dietary regimen without supplementary ascorbic acid five became symptom free and three improved The response was as satisfactory in the controls as in the experimental group Of the 22 patients in both groups 20 were benefited to a varying degree 11 *being completely relieved of symptoms* There was no objective evidence that the course was altered in any way by saturation with vitamin C but in nearly every instance patients expressed a feeling of increased well being at or near the point of saturation

Medical Aspects of Rehabilitation of the Tuberculous Louis E Siltzbach[1] (New York City) reports on 964 patients with pulmonary tuberculosis discharged from

(9) Am J Tuberc 4 548 60 Jun 1943
(1) Ibid 46 489 14 November 191

coal mines regardless of the average dust exposure Only two cases were found among persons with a known average weighted dust exposure of less than 20 000 000 particles per cu ft of air If persons with a dust exposure greater than this are considered the incidence of anthracosilicosis increases from 4 per cent for those employed 10 19 years to 11 per cent for those employed 20 29 years to 50 per cent for those employed 30 or more years All of these 16 men had been employed principally in underground occupations It is thought that their free silica exposure resulted from work at the coal face which involved handling coal containing bony from rock dusting and from dispersion of fine sand in the haulageways Ventilation studies showed that although each of the mines was supplied with air much in excess of the 150 cu ft per minute required by the Industrial Commission of Utah more than half the working faces had air velocities of less than 40 ft per minute and the air movement in some working places was practically zero

Engineering control methods which involve the thorough use of water at the point of dust generation and adequate ventilation of working places are effective in reducing dust concentration so that no exposure need exceed 10 000 000 particles per cu ft of air In addition to wetting the filled coal cars the road bed itself should be sprinkled wherever sand has been used since such sand contains a high percentage of free silica

Problem of Beryllium Dust Pneumonia is discussed by H Wurm and H Ruger[3] (Wiesbaden) on the basis of histologic study of lung tissue Macroscopic section showed a hemorrhagic pneumonic infiltration an atypical chronic pneumonia partially interstitial Microscopic study showed a chronic large cell carnified alveolitis which was somewhat similar to that in lungs affected with chromsilicosis described by Letterer To prove

(3) B lt Kl d T b k. 93 396 1942

at the end of the same period The mortality rate for the entire group at Altro was about twice that of the general population The patients with minimal lesions on admission to Altro had a death rate equal to that of the general population, those with moderately advanced lesions 1½ times that of the general population and those with far advanced lesions 4 times that of the general population At the end of 10 years 86 per cent of the patients with minimal disease on admission to Altro escaped recurrence or breakdown, 70 per cent of those with advanced lesions and 45 per cent of those with far advanced lesions had no recurrence For the patients with negative sputum on admission to Altro, 86 93 per cent of the first 15 years after discharge were spent as "well" years

PNEUMOCONIOSIS

Anthracosilicosis among Bituminous Coal Miners Robert H Flinn, Harry E Seifert and Hugh P Brinton (U S Pub Health Service) report that 16 cases of anthracosilicosis were found among 507 mine workers in Utah whose only occupational dust exposure had been in bituminous coal mines The patients were not seriously disabled Only one moderately advanced (second stage) case was found and no well advanced (third stage) case The degrees of pulmonary fibrosis as shown by x ray changes in the lung field markings of these individuals were similar to those in anthracite workers with early anthracosilicosis The bilateral massive conglomerate x ray shadows indicating advanced silicosis seen in 3 9 per cent of workers in Pennsylvania anthracite mines during a survey in 1934 were not observed in any of these bituminous coal mine workers

No case of anthracosilicosis occurred among workers with less than 10 years of employment in bituminous

(3) Indu t. Med 11 470-473 Octobe 194

coal mines regardless of the average dust exposure Only two cases were found among persons with a known average weighted dust exposure of less than 20 000 000 particles per cu ft of air If persons with a dust exposure greater than this are considered the incidence of anthracosilicosis increases from 4 per cent for those employed 10 19 years to 11 per cent for those employed 20 29 years to 50 per cent for those employed 30 or more years All of these 16 men had been employed principally in underground occupations It is thought that their free silica exposure resulted from work at the coal face which involved handling coal containing bony from rock dusting and from dispersion of fine sand in the haulageways Ventilation studies showed that although each of the mines was supplied with air much in excess of the 150 cu ft per minute required by the Industrial Commission of Utah more than half the working faces had air velocities of less than 40 ft per minute and the air movement in some working places was practically zero

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(3) Beit Kln d T b k 98 396 194

whether the changes were produced by beryllium dust animal experiments were carried out with dust of beryllium containing ore (silicate compounds) with the dust of pulverized smelting material (likewise beryllium silicate) and with beryllium hydroxide and beryllium oxide dusts The dust was mixed with physiologic sodium chloride solution and injected intratracheally In one group of animals left sided pneumothorax was per formed before the dust injection to compare the findings in the right lung with those of the left With beryllium hydroxide and the smelting dust a large cell alveolitis could be produced which without previous fibrin exu date could lead to extensive carnification This definite productive alveolitis also seen in man has not been ob served in other conditions The dust of beryllium con taining ore led only to physiologic changes

[Beryllium is used in the manufacture of fluorescent lamps A few cases have been observed in this country in which damage to the lungs has apparently been caused by this substance or some other ingredient —Ed]

Lung Changes Caused by Aluminum Dust are dis cussed by H Seidel [4] Existence of aluminosis previous ly was denied but Goralewski observed lung changes both in experimental animals and in workers in an alu minum factory that changed this concept Of 125 work ers 19 2 per cent showed certain and 31 2 per cent ques tionable lung disturbances On pathologic study Kahlau observed tissue degeneration and collagen hyaline forma tion in the parenchyma of the lungs with shrinking and induration Jaeger found an increased content of alu minum in the tissues Clinically aluminosis is charac terized by slight physical signs with extensive roentgen changes by *constriction of the lung capacity* breathing difficulty normal or slightly increased blood count nor mal leukocyte count with relative lymphocytosis and relatively rapid development and by the added occur rence of spontaneous pneumothorax That aluminosis of the lungs was not recognized earlier is explained by

(4) Ztschr f Tuberk 89 49 194

changed production methods in which small parts are ground more thoroughly and hence produce more dust and also by the fact that oiling during the stamping process has been discontinued

[Further study will be needed especially to ascertain whether the changes described are related to aluminum alone or to other contaminants —Ed]

Bagassosis An Industrial Lung Disease is described by L I M Castleden and J L Hamilton Paterson [5] Bagasse is the term applied to broken sugar cane after the sugar has been extracted it is now used in the manufacture of board The bagasse arrives in open bales which are then broken i e the raw material is crushed into small fragments The bale breaking is done by machinery giving rise to a great deal of finely divided dust The product is largely composed of fiber contains 1 per cent protein and 5 7 per cent silica Workers who feed the bales into the machines and the supervising engineers develop respiratory illness workers engaged in cutting and trimming the finished boards are not affected Four cases of bagassosis are described

Clinical appearance suggests an acute inflammatory lung disease with extreme dyspnea as the presenting symptom but with little or no febrile reaction In two cases complete resolution of the lung lesion took place in one case and probably in another the lesion is progressing to a fibrotic type Although bagasse contains silica the acute pneumonic phase of the illness is unlike any known form of silicosis A pathogenic organism has not been isolated from the sputum in the acute stage and examination of 15 consecutive 24 hour specimens of sputum from one case failed to disclose any yeast or fungus

It seemed possible that an allergic factor might be responsible the workers becoming sensitized to a protein in the dust of bagasse Intradermal tests with extract of bagasse produced positive reactions in the four patients and negative reactions in workers not working at the

(5) Brit M J 2 478 480 Oct 4 194

bale breaking machines It seems certain, therefore that whole bagasse contains an antigen soluble in normal saline to which workers who inhale the dust can become sensitized The acute phase of bagassosis is possibly an allergic response in the lungs to this antigen with but more probably without, an infective element The chronic pathologic process might be due to a form of silicosis which supervenes on the allergic phase during or after the latter s resolution a response of the lungs to crystal line cellulose or a chronic fibrotic process occurring in tissues made edematous by their allergic response to the antigen The last explanation of the lung changes may have a parallel in some of the more common chronic diseases whose etiology is obscure such as rheumatoid arthritis

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TRAUMA—PHYSICAL AND CHEMICAL

Symposium on the Cocoanut Grove Disaster Pul monary Complications A clinical description of the pulmonary lesions seen in the burned victims treated at Massachusetts General Hospital is presented by Joseph C Aub Helen Pittman and Austin M Brues[6] The first clue to the high incidence of pulmonary burns was afforded by the number of persons who died within the first few minutes after reaching the hospital They were extremely cyanotic, comatose or restless and had se vere upper respiratory damage There was little correla tion between the severity of surface burns and extent of pulmonary damage, and it was necessary to watch for pulmonary signs even in those who were only slightly burned Surviving patients on arrival showed varying degrees of restlessness or excitement but soon became quiet following medication and removal to the ward None was very cyanotic some were cherry red in color suggesting carbon monoxide inhalation Several more severely burned patients were delirious and two were

(6) Ann Su g 117 834 840 June, 1943

quieted promptly by oxygen inhalation About three hours after the fire dyspnea suddenly appeared in several patients associated with cyanosis restlessness and increased rales An oxygen tent promptly relieved cyanosis but had no effect on the dyspnea Complications in this stage were acute dilatation of the stomach in two a wildly delirious state apparently due to anoxia and auricular fibrillation in one case eventually relieved by oxygen administration A more critical period occurred about 24 hours after the fire and continued for the next 36 Dyspnea and cyanosis became much aggravated in certain patients and rales again spread this stage was obviously due to edema from burns of the upper air passages trachea and bronchial tree Following subsidence of the epidemic like attack of pulmonary edema the final subacute stage of pulmonary manifestations set in of which the pathologic basis was diffuse bronchiolitis This resulted in obstruction of the air passages sufficient to produce localized lobular collapse and trapping of air at the apexes with acute emphysema

The lung complications encountered may be classified into four degrees of severity The patients were grouped on this basis as follows grade 1 9 patients with minimal abnormal physical signs manifested by rales and with no significant diminution of vital capacity grade 2 8 patients with rales and emphysema marked diminution in breath sounds together with roentgen evidence of trapping of air and slight diminution of vital capacity grade 3 7 patients with added persistent atelectasis attributed to edema sufficiently marked to obstruct the passage of air into certain areas of the lungs during either phase of respiration and reduction of vital capacity of varying degrees between the limits of 25 and 83 per cent of the theoretical normal grade 4 12 patients with the most severe degree of injury (7 died and 5 survived)

Experience following this disaster teaches (1) that

covering the mouth with a wet cloth may afford complete protection against pulmonary burns (2) that in most patients the degree of inhalation burn was not ascertainable immediately after the fire and the extreme edema which occurred later could not be predicted (3) that the resuscitation of patients in acute attacks of edema was difficult and unsatisfactory, and that these acute attacks must be watched for with great vigilance even in patients with minimal surface burns

The pulmonary complications were bizarre and characterized by extreme variability with areas of lung collapse and emphysema often quite transient and migratory As injury to the bronchioli healed these signs disappeared and the lungs sounded as though no permanent damage had occurred Roentgen examination confirmed this but only time will tell whether bronchial scars will constrict and produce bronchiectasis in the future

Richard Schatzki reports on the roentgen study of these pulmonary lesions Thirty five of the survivors were examined roentgenologically Pulmonary changes were found at some time in 22 patients whereas examination of the other 13 was negative at all times The roentgen appearance of the lungs was bizarre and varied from patient to patient Most lesions however could be explained by areas of atelectasis and emphysema both apparently due to bronchial occlusion particularly of the smaller bronchi Atypical lesions (miliary nodules and areas of drowned lung) were seen in a few cases Diffuse pulmonary edema was found in two victims dead on arrival Pulmonary lesions of all the survivors finally disappeared except in two cases

Tracy B Mallory and William J Brickley[8] report on the pathologic findings in six of the victims Three of the patients were dead on arrival at the hospital and the other three died 40 62 hours later Cutaneous burns of

(7) Ann Surg 11 841 864 Jun 1943
(8) Ibid pp 86 934

first second and third degree were common to all the burns were particularly severe about the head In all cases the total area of cutaneous involvement was insufficient to account for death within the brief time before the patients reached the hospital The three patients dead on arrival showed a brilliant cherry red discoloration of the muscles and blood rich viscera suggesting the probability of carbon monoxide poisoning There were also intense but non necrotizing hemorrhagic tracheitis and bronchitis and heavy voluminous lungs from which large amounts of fluid could be expressed Microscopic examination confirmed the presence of acute pulmonary edema and demonstrated in the upper tracheobronchial tree a serohemorrhagic exudation without significant leukocytic infiltration The mechanism of death was anoxemia dependent partly on inhalation of carbon monoxide and probably other gases and partly on edema of the lungs

The three patients who died after hospitalization exhibited *similar distribution and extent of cutaneous* burns The major visceral lesions were again found in the respiratory tract In two there was severe necrotizing laryngitis with formation of a pseudodiphtheric membrane leading to almost complete laryngeal stenosis All three showed diffuse hemorrhagic and focal membranous reaction in the lower trachea and primary bronchi with diffuse membranous bronchitis most severe in the secondary and tertiary subdivisions of the lobar bronchi but extending to the smallest bronchioles

Microscopic examination showed diffuse necrosis of the lining epithelium In many areas the shadow forms of *the necrotic cells rested in situ on the intact basement* membrane Accumulation of small lakes of serum between this layer and the basement membrane gave a clue to the mechanism of spontaneous detachment In other areas all traces of the epithelium had disappeared and a dense rather hyaline fibrinous membrane rested on an intact basement membrane In the larynx and trachea

but rarely in the bronchi evidence of deeper necrosis was found, but even in these areas the zone of necrosis was not deep never wider than 100 microns

The pulmonary lesions varied considerably from case



F - 3- (top) — B onchu l men plug- d by desquamated ells fib in d leuko t s most of b me t m mi ane denud d but some rem e tin epithelial lls an be en o l ft

Fig 83 (bottom) — Sam as Pa i lly collaps d al e li co taini rou pre p t te and a few leuko yt pirat ty b o hi les i ned with a ll e s fibrino d memb ne

to case and included anatomic emphysema with super imposed acute pulmonary edema extensive atelectasis and compensating physiologic emphysema and massive hemorrhage into the alveoli of large atelectatic areas Atelectasis and compensatory physiologic emphysema dominated the picture in one case (Figs 32 33 and 34) Multiple small emboli were found throughout the lung in normal as well as in abnormal areas Small foci of



F 34 — m p eced g Art l f m rr l p rt f l ng h wa dh nt th hy l mb l lu pe l lymph t w d ly d l t d m l mbol w e m u n th

hemorrhage usually only of lobular dimensions were present some were typical of infarction others showed viable alveolar walls Widespread foci of incipient bronchopneumonia were present within the areas of atelectasis but the evidence suggested that this pneumonic reaction was very brief

Other organs with few exceptions showed no abnormalities attributable to the acute incident An exception was focal necrosis of the adrenal cortex in two cases and changes attributable to prolonged anoxemia also present in two cases

It is difficult to account for the massive pulmonary

edema which must have developed extremely rapidly Perhaps a combination of anoxemia and some irritant may have worked synergistically in these cases The most characteristic feature of the pathologic study was the diffuse membranous bronchitis which constitutes the strongest evidence for inhalation of toxic fumes

Pathology of Closed Injuries of Chest J V Wilson[9] (R A M C) reviews his experience with postmortem examination of battle casualties Closed injuries of the chest are divided into those caused by direct violence like lacerations contusions and blast injuries and those resulting from injuries elsewhere in the body like fat embolism

The severity of lung laceration depends less on the actual lung injury than on possible complications Laceration of the lung rarely causes death in itself a hematoma forms around the actual tear (usually from fractured ribs driven in) but owing to collapse of lung tissue hemorrhage soon stops Various complications may occur (1) Pneumohemothorax is rare for the clot seals off the alveoli and subpleural bullae are rarely extensive and seldom rupture Hemothorax is common and may be extensive It may originate from bleeding from the intercostal and mammary vessels or from the pulmonary vessels at the site of laceration (2) Compression or collapse of lungs may be acute in pneumothorax or gradual in hemothorax The heart is pushed to the other side and circulation and aeration of the opposite lung are severely impaired Massive collapse is rare and is probably due to loss of cough reflex through shock or pain and consequent collection of secretion and blockage of a bronchus (3) Infection is still a major complication despite use of sulfonamides The pleura is rarely infected until later but pneumonic changes may be early

Contusions occur chiefly in younger persons whose ribs are still elastic and the underlying structures

(9) Brit M J 1 4 0474 Ap 1 1943

heart and lungs may be contused without fracture of ribs The lung directly hit shows hemorrhage but the opposite lung receives contrecoup injuries identical with those found in pulmonary concussion

With blast injuries the lung picture is usually one of hemorrhage The hemorrhages are scattered throughout the lung in deep and subpleural areas There is no suggestion of consolidation and the lungs feel rubbery Dark linear markings are present in adults as often as in children and correspond to intercostal spaces rather than to ribs especially in older persons The regions most affected are those which expand indirectly i e the posterior surface of the apex and of the lungs in contact with the spinal column and laterally the middle parts The microscopic picture is that of widely spread congestion and intra alveolar hemorrhage and edema An aspect of blast injuries which has received little attention is mediastinal trauma resulting in contusion of the heart rupture of the aorta and hemorrhages into the anterior mediastinum Direct trauma to the chest wall rather than positive or negative pressure wave is the most plausible theory which would account for simultaneous lung and mediastinal injury

Pulmonary fat embolism is usually a sequel of fracture of the femur Fat droplets can be seen in the capillaries and the alveoli contain red cells and edematous fluid red cells being less numerous but the edema much more pronounced than in blast injuries

Effect of Irritant Gases on the Rate of Ciliary Activity was studied by Lester V Cralley[1] (State Univ of Iowa) Rabbits were used since the ciliary response of the excised human and rabbit mucosa is similar The results led to the following conclusions Ciliated epithelium when kept in Ringer s solution tends definitely to become increasingly susceptible to the effect of an irritant gas (sulfur dioxide) with the lapse of time after its removal from the animal Excised tissue tested 7½

(1) J I d t Hyg & T 1 4 193 198 S pt mb 194

hours after removal from the animal was four times as sensitive as tissue studied within ½ hour after removal as shown by complete cessation of ciliary activity This time factor should be considered when studying excised tissue It was shown by comparison of the effect of sulfur dioxide on freshly excised rabbit tissue with the effect of the same gas on intact tissue in the human subject that the ratio of the response was the same The intensity of the response was greater with excised tissue The critical zone beyond which complete cessation of ciliary activity (excised tissue) takes place is relatively narrow as to concentration and as to time This critical zone in concentration of the gases studied was found to be as follows chlorine, sulfur dioxide and formaldehyde 30 p p m hydrogen chloride and nitrogen dioxide 60 p p m ammonia 400 p p m and hydrogen sulfide 500 p p m The immediate irritation of the throat on exposure to certain irritant gases offers a comparative index as to the depressing effect of these gases on freshly excised ciliated epithelium Exposure to small amounts of irritant gases for long periods may lead to a chronic irritation of the mucosa which would accordingly affect ciliary activity

[The following articles on the effects of pulmonary irritants should be considered in connection with the work of Drinker and his associates (this YEAR BOOK pp 157 and 159) The articles by Barach on the use of positive pressure gas therapy should also be consulted (this YEAR BOOK p .01) —Ed]

Pulmonary Irritants are discussed by Robert A Kehoe and Karl V Kitzmiller (Univ of Cincinnati) These comprise a group of compounds that exist as gases or liquids and have a sufficiently high vapor pressure to give rise to injurious concentrations in respired air They include (1) acid gases such as hydrogen chloride bromine and fluoride and chlorine bromine sulfur dioxide and certain oxides of nitrogen together with phosgene diphosgene and chloropicrin (2) vesicants such as mustard gas and lewisite which despite

( ) Cincinn ti J Med 23 423 443 No mber 194

their low vapor pressure give rise at ordinary temperatures to highly irritant concentrations of vapor Inhalation of ammonia or formaldehyde in sufficiently high concentrations may cause upper respiratory and pulmonary irritation Iron and nickel carbonyl may be classified as pulmonary irritants because of their property of depositing finely divided particles of metal in lung tissue

The initial symptoms of exposure to irritant gases are sharp burning pain in the eyes nose and throat with constriction of the throat and irregular respiration followed by rapid dyspneic respiration and subsequently by some degree of relief as the secretions of the eyes and nose begin to flow and bathe the irritated surface Labored breathing with spasmodic coughing may be marked and chest constriction and pain with air hunger and the fear of impending death may develop On escape from exposures of less than extreme severity there is some relief but coughing continues for some time producing blood tinged or frankly hemorrhagic sputum After 2 to 12 hours of relative comfort respiratory distress accompanied by increasing physical signs of pulmonary moisture may begin to develop and may reach an acute stage promptly especially on exertion or there may be a gradual subsidence of all symptoms The 24 hours following exposure is the crucial period during which the patient should be kept quiet and warm Specific measures for prevention of pulmonary edema will also probably be indicated if and when such measures can be developed on a sound physiologic rationale Persons who do not develop pulmonary edema within the first 24 hours usually recover promptly while those who develop it may be ill for a few days to many weeks Secondary infection through invasion of the bacterial flora of the nose and throat into the injured tissues may be expected to develop and infectious tracheitis bronchitis bronchopulmonary abscess and bronchopneumonia are likely to follow Death may occur at any of these stages Onset

of pulmonary edema may be prompt or delayed for as long as 12 hours In the young and healthy the longer its appearance is delayed the less likely it is to develop The outlook is uncertain in the old and in persons with chronic respiratory and circulatory diseases

Exposure to chlorine results in acute painful injury to the upper respiratory tract together with somewhat less serious damage to the lungs Pulmonary edema develops with little or no delay and reaches its climax within 12 to 24 hours Exposure to phosgene cause little upper respiratory tract injury and there is a latent period of apparent comfort before pulmonary edema develops The edema develops rapidly however after onset most deaths occurring within the first 24-48 hours Delayed deaths occur as a result of pneumonia or toxic damage to the heart muscle brain liver and kidney Exposure to chloropicrin causes less injury to the upper respiratory tract than chlorine and more than phosgene An acute bronchitis develops early as a result of injury to the medium and small sized bronchi Pulmonary edema also develops promptly Exposure to mustard gas produces acute injury and inflammation of the entire respiratory tract followed by necrosis and desquamation of the mucous membrane and pulmonary epithelium A diphtheric membrane forms on a mucous surface and a lobular pneumonitis develops with plugging of the bronchioles followed by formation of bronchopulmonary abscesses that quickly come to the surface inducing pleuritis and locular empyema Generalized pulmonary edema is not a conspicuous part of the picture Clinical information on the effects of lewisite in humans is not available From observations on dogs it seems that the effect is similar to that of mustard gas except that greater pulmonary edema is produced

The clinical types of pulmonary edema produced regardless of the responsible agent have been differentiated as (1) latent type (2) blue ' cyanotic type and (3) "gray ' or pallid type In blue cyanosis the individ

ual has an anoxemia sufficient to give rise to cyanosis and therefore is suffering from some degree of tissue anoxia Gray cyanosis when it appears early in the course of illness denotes either extensive pulmonary damage or a crippled circulatory system When seen as a late manifestation it is a sign of cardiac weakness

The experience of World War I has shown that complete recovery was the rule among young healthy persons who survived the acute effects of exposure to pulmonary irritant gases The sequelae that have been described among soldiers are pulmonary fibrosis chronic emphysema chronic bronchitis and bronchiectasis—all results of infection rather than chemical injury—together with two other disturbances which are partially functional namely the effort syndrome and nocturnal dyspnea

First aid treatment of casualties consists of maintenance of quiet and warmth until transportation in a recumbent position can be accomplished The patients should not be permitted to walk or even to sit up should be covered with blankets and given warm drinks Artificial respiration should not be given even to persons in acute respiratory distress and decontamination should be limited to simple quickly completed measures such as clipping of hair cutting away of clothing and removal of any agent dangerous to life or vision No treatment for prevention or relief of pulmonary edema is available Relief of the anoxia may be obtained in many cases with oxygen Use of the nasal catheter is best when special equipment is not available Relief of high venous pressure associated with florid or blue cyanosis may be obtained by venesection but little benefit can accrue from attempts at blood letting during gray cyanosis Use of sulfonamides may offer means to cope with the infections which follow upper respiratory and pulmonary injury Arsenicals may be indicated in pulmonary abscess with gangrene associated with spirochetal infections Other forms of treatment are nonspecific and in

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in the bronchi, there is no advantage in using helium. Helium will pass through small bronchi easier than nitrogen, but it will not increase the solubility of oxygen in edema fluid of the alveoli and bronchi. Therefore oxygen helium mixtures are not recommended. (2) Bronchiolar obstruction possibly bronchiolar spasm. This is recognized by asthmatic rales and acute emphysema and is treated like asthma (3) Hemoconcentration due to loss of plasma from the effective blood volume It is recognized by livid cyanosis and black thick blood on bleeding and by high red blood cell counts and is best treated by plasma unless the latter is found to increase pulmonary edema. (4) Obstruction to blood flow through the lungs It is recognized by engorged neck veins, high venous pressure on bleeding and the precordial signs of right heart failure and is treated by bleeding (5) Shock partly due to hemoconcentration and anoxia and partly to the effects of gas on the central nervous system It is recognized by low blood pressure, failing pulse and ashen cyanosis Treatment with paredrinol adrenal cortex extract and desoxycorticosterone acetate together with plasma deserves a trial Morphine to reduce anxiety and pain is recommended unless there are severe cyanosis and slowed respirations

The late effects of pulmonary irritants are complicated by infection i e tracheitis bronchitis and pneumonia Treatment of pneumonia following gassing does not differ from that of any other type of pneumonia except the pneumonia following mustard gas corrosion of the trachea and bronchi In these cases severe pain and cough require attention and postural drainage must be practiced periodically to clear the large air passages Also loculated pleural effusions occur with great frequency and may be infected early in the course of pneumonia These early multiple and scattered loculated empyemas must be discovered and treated by aspiration or even by drainage

The prognosis in gassing can generally be decided after

clude general supportive treatment and careful supervision to assure that the patient avoids overexertion

Therapy of Pulmonary Irritant Gases To treat pulmonary irritation produced by these substances M. A Blankenhorn[3] (Univ of Cincinnati) states that it is not essential to know precisely what gas has been inhaled, for there is no specific antidote and the disease resulting from each is much the same Pulmonary irritation depends on dosage, i e, large doses cause immediate and lethal effects and smaller (less concentrated) doses later but deeper irritation which may or may not be lethal Large or small doses of acid gases cause corrosive effects when they come in contact with moist respiratory membranes which may be mild leading to edema, or severe ending with necrosis If these acid effects are not directly and promptly lethal infection develops in the corroded tissues as in any thermal or chemical burn

The first aid stations should be mainly concerned with diagnosis and collection of casualties and with decontamination of the skin and clothing which is usually more urgent than medical treatment of pulmonary irritation Complete rest lying down must be rigidly enforced This applies also during transportation Medical treatment is such as is suited to severe pulmonary edema where the underlying cause is beyond control even though well known To guide this effort certain physiologic considerations gained from World War I experience and from animal experiments are helpful Five dangerous conditions may develop (1) Anoxemia due to moisture in the alveoli and bronchi It is recognized by cyanosis dyspnea rales and foaming sputum and should be treated by continuous inhalation of oxygen as long as cyanosis persists which may be several days Oxygen under pressure of a few centimeters (10 or less) of water may be more effective than oxygen at atmosphere Unless bronchiolar spasm is more apparent than moisture

(3) Ohio State M J 39 113 116 February 1943

guished by biopsy a hydatid cyst by eosinophilia and the Casoni test and Assmann s tuberculous foci by their subclavicular location and often associated adjacent minute flecks of infiltration or by cavitation Early radical treatment of benign tumors by local excision or by dissection lobectomy is the method of choice

Benign bronchial tumors although they may cause signs and symptoms originating from their very presence always cause signs of bronchial obstruction at a later stage In the early stage recurring hemoptysis irritable unproductive cough and attacks of dyspnea may lead to diagnosis During the stage of partial obstruction emphysema localized to the area of the lung distal to the growth is an infrequent but important physical and radiologic sign Stridor and wheezing may then be apparent Recurrent attacks of pulmonary infection usually in the same site are commonly encountered in the history Radiologic examination in an early stage will not show an abnormality unless the extrabronchial portion of the tumor is sufficiently large to show as an opacity in the lung Bronchography may demonstrate the growth before obstruction is complete Tomography may be of help However the only method of establishing the diagnosis with certainty is examination of a biopsy specimen removed by bronchoscopy Bronchoscopic examination is therefore essential in suspected cases As compared with malignant bronchial tumors there is little or no infiltration of surrounding structures the bronchus is movable local deformation of the trachea and main bronchi is absent and the benign growths bleed easily when touched

A review of the histories of 82 cases of bronchial carcinoma revealed that in 37 suggestive and significant symptoms had been present for six months or more at the time of diagnosis These were dry irritating cough worse in the morning and on exposure to cold air hemoptysis usually slight but occasionally quite free vague ill health upper abdominal discomfort unrelated

72 hours unless bronchopneumonia develops The convalescence in uncomplicated cases is determined by the probable damage to the myocardium

Oxygen under Pressure in Carbon Monoxide Poisoning Edgar End and Chester W Long[4] (Marquette Univ) state that carbon monoxide causes tissue damage by producing anoxia The current methods of treatment are unable to correct the anoxia Inhalation of oxygen under three atmospheres of pressure is capable of preventing it by causing solution of enough oxygen in the blood to provide for the needs of the tissues Inhalation of oxygen under this pressure for several hours is safe In the present experiments guinea pigs and dogs poisoned with carbon monoxide were quickly restored to consciousness by inhaling oxygen under pressure This is taken to indicate that their anoxia had been corrected Such treatment also accelerates elimination of carbon monoxide so that 30 minutes treatment proved ample to remove most of the carbon monoxide from the animals bodies It is proposed to introduce inhalation of oxygen under pressure in treatment of human beings severely poisoned by carbon monoxide

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NEW GROWTHS

Early Diagnosis of New Growths of the Lung is outlined by W D W Brooks (M C R N V R) As a class benign growths of the lung are symptomless until bronchial ulceration occurs with resulting hemoptysis and later possibly infection of the growth itself or until the increasing size of the lesion gives rise to pleurisy or to pressure effects on neighboring structures Radiologically they are easily shown as clearcut somewhat spherical or lobulated opacities and in the case of chondroma often showing irregular calcification or ossification From the viewpoint of differential diagnosis peripheral bronchial carcinoma can at an early stage only be distin

(4) J I dust Hyg & To col 24 30^ 306 Decembe 194
(5) P ct t ner 150 75 81 February 1943

evidence of both entodermal and mesodermal origin was revealed by areas of varied predominance of one or the other derivative In the third case in a man 34 with suggestive signs of an intrabronchial tumor including hemoptysis less evidence of origin from mixed dermal layers was observed in each of the two tissues removed for biopsy Comparison however of the two specimens between which there was an interval of four years revealed a definite emphasis on mesodermal structure in the first while an entodermal character was clearly shown in the latter specimen The neoplasm in the second biopsy conformed closely in histologic aspect to embryonal glands The fourth case was in a patient 19 with a history of occasional hemoptysis since age 7 Other clinical signs and symptoms were those usually present in a persistent intrabronchial polypoid growth with ball valve action The specimen obtained through the bronchoscope presented a neoplasm of mixed dermal components as revealed by prevalence of elements of both layers

It seems imperative from the standpoint of histologic study of bronchiogenic tumors that the embryologic nature as emphasized by Womack and Graham must receive serious consideration While the biologic characteristics of malignancy or benignancy are more or less constant regardless of the primary nature or embryonal origin of neoplasms there are precedents for a benign nature of many tumors of the latter origin These serve to promote conservatism in evaluation of the relative malignancy of the pulmonary growths which may belong to this group

Successful Removal of Hemangioma of the Lung Followed by Disappearance of Polycythemia is reported by John Hepburn and James A Dauphinee[7] (Univ of Toronto)

Woman 23 complained of dizziness faintness and thick speech She presented marked cyanosis clubbing of fingers and some diminution of movement and lung resonance in the

(7) Am J M S 04 681 685 N mber 194

to exertion or food, and persistent or intermittent slight pain felt deep in the chest It is suggested that when one or more of these symptoms arise in a middle aged male he should be fully investigated Radiologic examination will disclose at an early stage, long before any signs are present those bronchial carcinomas which arise peripherally in the lung and which constitute about one fifth of these tumors The others, however, arising in major bronchi do not give radiologic evidence until the disease is advanced Bronchography may reveal a growth by showing an abnormal bronchial outline before obstruction has occurred Tomography may define intra and extrabronchial components of the lesion and presence of mediastinal secondary lesions Examination of the sputum by the method of Dudgeon may demonstrate malignant cells in 60 per cent of cases Bronchoscopic examination will reveal nearly 80 per cent of bronchial carcinomas and give information as to the usefulness of surgical intervention In cases of partial or complete bronchial occlusion due to external location of the growth bronchoscopy is only rarely helpful in obtaining histologic proof of the nature of the lesion and in these cases and others in which there is hope of successful surgery, exploratory thoracotomy should be done

[*We have not had much success in searching the sputum for tumor cells —Ed*]

Anlagen and Rest Tumors of the Lung Inclusive of Mixed Tumors (Womack and Graham) William H Harris and Herbert J Schattenberg[6] (Tulane Univ) report on four tumors of the lung manifesting distinct evidence of origin either in anlagen or from more than one germinal layer The first two tumors occurred in new born full term infants who survived seven and five days respectively In the first case embryonal bronchial budding was perpetuated in a neoplastic mass This was demonstrated by an aimless reduplication of tubular and immature alveolar structures indicating a lack of orderly sequence of bud branching In the second case

(6) Am J Path 18 955 987 September 1942

and cough reflexes the more direct course of the right bronchus and gravitation of infected secretions to the right side reduction in bronchial ciliary action by the mass of secretion weakening of the abdominal muscles by the incision and splinting of the diaphragm and the lower lobes of the lung by retraction upward and to the right During spinal anesthesia for abdominal operations the same handicaps of incision and retraction obtain and in addition paralysis of the lower intercostal muscles causes reduced pulmonary ventilation In operations on the kidney or lung the side opposite that operated on is splinted by the weight of the body and secretions gravitate into the lower lung

Prolonged anesthesia should be avoided During general anesthesia the upper respiratory tract should be kept free from excessive secretions by aspiration through a catheter If possible the Trendelenburg position should be used The head of the operating table should be inclined 10 degrees or more In all cases of pneumonectomy a roentgenogram should be taken while the patient is on the operating table immediately after the wound is closed and if atelectasis is disclosed in the remaining lung bronchoscopic aspiration of the lung is performed at once After the patient is returned to his room he should be turned frequently and perform deep breathing exercises Hyperventilation with oxygen and carbon dioxide stimulates deep breathing Abdominal binders should be kept below the level of the thorax Excessive postoperative use of narcotics should be avoided so as not to depress the cough reflex and respiratory center Two weeks if possible should elapse after an acute respiratory infection before an operation is done

In most instances atelectasis can be successfully treated by hyperventilation deep breathing exercises and raising of bronchial secretion by coughing If prompt relief does not occur bronchial catheterization or bronchoscopic aspiration should be done Complications are postoperative pneumonia and pulmonary abscess

right scapular region but no bruit was heard Blood examination showed marked polycythemia hemoglobin being 140 146 per cent and red cell count 9,000 000 9,600,000 per cu mm packed cell volume 80 per cent, total blood volume 8 500 cc vital capacity was 1 700 cc Fluoroscopic and roentgen examinations revealed a shadow in the right middle and lower lobes. It was felt that the cyanosis was not secondary to polycythemia since it had been present before any increase in red cells or hemoglobin had occurred and was central rather than peripheral in origin This was attested by the observation that when the patient s hand was immersed for 10 minutes in a water bath at 45 to 47 C it became uniformly and more deeply cyanosed and by the fact that peripheral arterial oxygen saturation was only 70 75 per cent Since she presented no evidence of congenital heart disease and no suggestion of any generalized pulmonary disease but did show a circumscribed local lesion in the lung on roentgen examination it was assumed that she had an abnormal arteriovenous communication in the lung in the nature of a cavernous hemangioma

An attempt was made by artificial pneumothorax to close this arteriovenous communication in the lung but, although good collapse was obtained no change could be noted in the degree of cyanosis and no increase in arterial oxygen saturation Pneumonectomy was then performed Pathologic diagnosis was cavernous angioma of the lung Operation was followed by an immediate cessation of cyanosis a rapid return of normal oxygen saturation of the arterial blood, rapid disappearance of polycythemia more gradual disappearance of clubbing of the fingers and after a short period, definite improvement in general health

Postoperative Atelectasis Herbert W Schmidt Lloyd H Mousel and Stuart W Harrington[9] (Mayo Clinic) state that atelectasis may complicate convalescence from any operation and is the commonest pulmonary complication after abdominal operation It almost always develops as a result of decreased pulmonary ventilation and inadequate endobronchial drainage The more remote causes are the anesthetic agent position during operation and type of operation During operations on the upper part of the abdomen under general anesthesia the following factors may be operative in producing atelectasis abolition of the laryngeal

(9) J A M A 1 0 895 900 N v 1 194

and cough reflexes the more direct course of the right bronchus and gravitation of infected secretions to the right side reduction in bronchial ciliary action by the mass of secretion weakening of the abdominal muscles by the incision and splinting of the diaphragm and the lower lobes of the lung by retraction upward and to the right During spinal anesthesia for abdominal operations the same handicaps of incision and retraction obtain and in addition paralysis of the lower intercostal muscles causes reduced pulmonary ventilation In operations on the kidney or lung the side opposite that operated on is splinted by the weight of the body and secretions gravitate into the lower lung

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In 84 selected cases of atelectasis, 58 in men and 26 in women average age was 50 In 52, operations were on the biliary tract or stomach in 9 on the colon and in 8 on the kidney and surrounding tissues In all cases in which atelectasis followed operation on the kidney, the lung affected was the one corresponding to the side on which the patient was lying If treatment was started within 48 hours after the complication occurred results were excellent If the complication existed for 72 hours or longer treatment was less effective, for secondary pneumonia had developed

[The term atelectasis as u ed here and frequently also by other authors does not describe the condition adequately Collapse of pulmonary alveoli alone does not predispose to pneumonia The accumulation and stagnation of edema fluid bronchial secretions and possibly aspirated matter in the bronchi and alveoli provide the medium for implantation and growth of bacteria and the re sultant pneumonia —Ed]

MISCELLANEOUS

***Echinococcus* Cyst of the Lung** William A Evans Jr [9] (Detroit) reports a case which illustrates a pathog nomonic roentgen sign

Italian boy 12, complained of pain in the left chest and cough for 10 days He had had a similar attack the previous year There was some dulness on percussion in the left chest posteri orly, with diminished breath sounds and fine rales No eosinophilia was present X rays disclosed a sharply circum scribed shadow in the left midchest posteriorly, measuring 10 5×8.5 cm (Figs 35 and 36) The shadow was of uniform density except for the appearance of a capsule at the periph ery, with a layer of air between the capsule and the mass The phenomenon was not explained, and presumptive diagnosis was benign tumor A week later, following production of a diagnostic pneumothorax air was no longer seen beneath the capsule In a third study immediately preceding operation, the pneumothorax had disappeared and there was no sign of a cap ule or any other differentiating shadow in the mass On operation a cyst was found in the periphery of the left lower lobe and removed and a bronchial fistula deep in the pouch

(9) R di logy 40 36 366 Ap il 1943

containing the cyst was closed Recovery was uneventful

As the echinococcus cyst enlarges bronchial communication may develop in the adventitia and on coughing or other forceful expiration a small amount of air may enter the space between the membrane of the hydatid vesicle and the adventitia of the host Like the intrapleural cavity this space is originally present as potential only The phenomenon is rare but is pathognomonic when it does occur Although the pericystic air space is reversible it usually indicates imminent disintegration and rupture of the vesicle and subsequent evacuation of the cystic fluid and membranes through a bronchus (vomica) Figure 37 illustrates the stages of disintegration of a pulmonary hydatid cyst When the cyst ruptures the fluid becomes infected and differentiation from a lung abscess may become difficult Recognition of the retained membrane the slow movement of fluid on change of position and expectoration of fragments of



F g 35 (l ft) —P t o- ter film h l d m f hyd tid l ep ted f m p l f d t t b cr t p sup rio ly nd to l se ext nt inf ri ly

F 36 (ght) —R ht l t l film f m

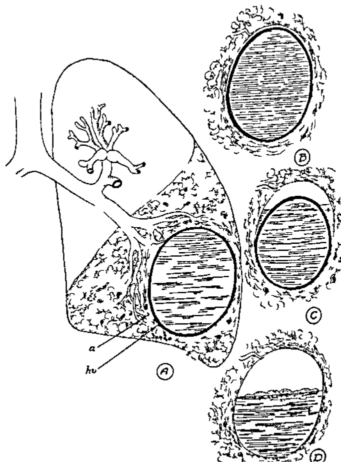


Fig 37 —Diagr m of stages n d i teg ti n of pulmonary hyd tid cyst *a* adventitia ontaini g t l ctatic alveol a d comp sed b onchioles *hv* hyd tid ve le with wall in l app t n to d e t t *Stage A* adve t tia a d hydat d v s cle int t p t ve roentgen di gn is c n a ely be m de S gn of E cud o N me o (change h pe f hadow d i g r spirat n) and Q e lo-W l ch (e p ns n f i volved s e f hest) may be h lpful *Stage B* a ha ente ed sp between ad t tia a d hydat d ve icl by means of b nchi l commu ic t n y od ing sign of det chm nt or per ves cul p eumo y t f M rqui Bonaba d Soto *St ge C* f rth r separat on of y t and dve t t a d sintegrat n of y t has pe mitted le kage of cyst fluid into pe cy tic spa e (Cumbo sign double c ign of Ivan ev h) *Stag D* collap f cyst compl te a d r tai ed membra e floats on cystic flu d p ducing the water l ly sign of Sez rs a d Lago Ga ci At thi stage cy tic fl id is usually seco da ily infe ted a d purulent e pulsion of fl id and memb anes th o gh a b o ch m o ur d i g se e

the membrane with identifiable hooklets may be valuable aids in making an accurate diagnosis

Lung Stone Causing Profuse and Recurrent Hemoptysis is described in a case reported by F G Chandler[1] (London)

Woman, 35 had had daily attack of coughing for 20 years dating from an attack of pneumonia Once or twice a year she had severe hemorrhages from the lungs She felt well otherwise and had lost no weight Soon after a provisional diagnosis of bronchiecta is was made on the basis of dulness and rales over the right lower lobe the patient had a severe attack of coughing which produced an irregular hard jagged object 0 75 × 0 5 cm in size apparently a lung stone A profuse hemorrhage followed immediately The daily coughing spells ceased Subsequent investigation with lipiodol showed no bronchiectasis

The patient was followed for eight years during which time she had three slight hemorrhages after heavy exertion but no cough The following year she had pneumonia on the left side followed by empyema which was successfully drained While in the hospital for drainage she had a coughing and vomiting attack and brought up a stone similar to the other one but smaller She made an excellent recovery and has remained well and without hemorrhages for three years

[Thes bronc ol ti s ar usually ale fi l tul erculous masse They may develop in the lymph nodes and later rode into a bronchus acting much like a foreign body Sometimes if ther ar conne ted ca ous foc the bleeding may carry tubercle bac lli to the lung causing ne v les ons there —Ed]

Pyogenic Osteomyelitis of Thoracic Spine Presenting as Primary Pulmonary Disease In the developing clinical picture of pyogenic osteomyelitis of the spine the paravertebral complications local or distant may appear as the primary condition while destruction of the spine may progress extensively and remain unrecognized In any case with high fever pain in the back over the spine and roentgen evidence of mediastinal widening (mediastinitis) the possibility of pyogenic dorsal vertebral osteomyelitis should be excluded regardless of pulmonary signs symptoms or roentgenographic appearances and despite failure to demonstrate vertebral changes on roentgenograms Harry A

(1) L t 13 14 J 1 3 1943

Solomon and Arnold L Bachman (Bellevue Hosp) report the following illustrative case

In a man 33, from the onset and through seven months of hospitalization, clinical findings suggested a tentative diagnosis of primary inflammatory disease of the lungs Constant manifestations were pain in the chest and back of the chest, severe cough, profuse expectoration, frequent and severe hemoptysis, dyspnea and sepsis An early roentgenogram (Fig 38) revealed



Fig 38 —La g den e had w n m dlung field mall tr ngul opac ty at root of right lung

a large dense shadow in the left midlung field, interpreted as consolidation Roentgenograms of the dorsal and lumbar spine were reported as negative Bronchographic examination suggested left upper lobe bronchiectasis Pain in the chest continued and that in the back became more severe was medial and unaffected by respiration Mediastinitis on the right became definitely apparent on roentgenograms after hospitalization five months after onset Because of the opacity in the left lung field and lack of positive findings on roentgenograms of the spine, complication of osteomyelitis of the spine was not considered instead diagnosis of mediastinal lymphoma was made Severe interscapular pain over the dorsal spine increased and

(2) Am J Roentge l 49 19 ^6 Febru ry 1943

tenderness was elicited over the spine in this region There were weakness of arms and atrophy of small muscles of the hands Deep roentgen therapy to the supposed mediastinal lymphoma was soon followed by pointing of the mediastinal suppuration with paravertebral abscess formation Roentgen evidence of osteomyelitis with destruction of the dorsal vertebrae finally became apparent at the same time seven months after onset Incision and drainage were of no avail and the patient died nine months after onset Besides extensive destruction of the dorsal spine autopsy disclosed suppurative mediastinitis atelectasis of the left lung and compensatory emphysema of the right lung

In retrospect it was realized that one significant sign was present throughout the illness namely the fixed supine position which the patient constantly assumed

Idiopathic Progressive Brown Induration of the Lung in Childhood with Hereditary Hemoptysis Intermittent Secondary Anemia and Eosinophilia and Embolic Focal Nephritis is reported by E Glanzmann and B Walthard[3] (Univ of Bern) Under the term hereditary hemoptysis Libmann and Ottenberg in 1918 described a new form of hemorrhagic diathesis manifested by recurrent attacks of hemoptysis frequently thought to be of tuberculous origin However there were no pertinent pathologic signs in the lungs and no signs of hemophilia thrombopenic purpura or telangiectases in the upper air passages The disease is heredofamilial with a dominant trait It is benign in adults as it was in the father of the authors patient a girl aged 13

The most striking clinical feature is anemia at times marked (25 30 per cent hemoglobin) The pallor of the skin is mixed with yellow and there are a subicteric tinge to the sclera increased urobilinogen excretion in the urine leukopenia and eosinophilia Blood platelet count ranges from 140 000 to 90 000 The authors patient a child had a mild albuminuria and varying degrees of hematuria It was thought at first that the anemia was secondary to the loss of blood through the

(3) A p d t 157 54 57 1941

kidney Later however it was noted that she nearly always had a blood tinged sputum the hemoptyses were thus the true cause of the anemia Roentgenograms in these cases show a characteristic fine mottling in the hazy middle and lower lung fields reminiscent of Boeck's lung sarcoid miliary tuberculosis or silicosis The mottling is due to hemosiderosis of the lungs resulting from repeated hemoptyses The course of the disease is intermittent with severe (afebrile) crises of sudden progressive anemia and repeated vomiting with more or less admixture of the coughed up and swallowed blood Near the fatal termination which usually occurs two to three years after onset the crises become more frequent and are associated with extreme anemia progressive dyspnea irregular pulse and states of anxiety

Pathologic findings in the authors case consisted of extensive brown induration of the lungs or so called muscular cirrhosis The alveoli were filled with heart failure cells the intra alveolar septums were thickened and infiltrated and the broken elastic fibers were incrusted with iron deposits frequently being surrounded by giant cells in foreign body like fashion The heart showed no valvular disease The kidneys revealed embolic focal nephritis with partial necrosis of the glomerular loops and iron concretions

The disease presumably represents a constitutional pulmonary condition due to inherited weakness and defective development of the elastic fibers Lacking adequate support the pulmonary capillaries become distended and are not sufficiently emptied during the expiratory phase giving rise to congestion and hemorrhages into the alveoli which then become filled with heart failure cells in the absence of cardiac disease The recurrent hemoptyses lead to progressive brown induration and hemosiderosis of the lungs The iron concretions may as in the authors case be carried into the kidneys and there produce embolic focal nephritis

DISEASES *of the* BLOOD *and* BLOOD-FORMING ORGANS, DISEASES *of the* KIDNEY

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(Edinburgh and London)

AND

WILLIAM B CASTLE M D S M
M.D (Hon) Utrecht

PART III

DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS

GENEPAL CO\SIDERATIO\S

The articles presente l in this s et on are concerned with certa n general aspects of the d sorders of the blood and blood forming organs Included are art cles on h olog c technical and th rapeutic aspects wh ch apply to mo e than one of the subsequent sections —Eds

Simple Blood Cell Counter E E Myers and E E Beohm[1] (Philippi W Va) describe a method of recording the numbers of various cells in a differential count

METHOD —One hundred marbles are u ed and as many boxes as cell types A marble is dropped into the appropriate box

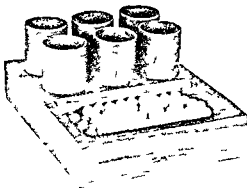


Fig 39

as each cell is identified When all the marbles are distributed the number in each box is counted to give the different cell percentage The number in the box containing the most mar

(1) Am J Cl I th 13 14 J rr 1943

bles is easily determined by subtracting the total of the others from 100 The easily constructed unit is shown in Figure 33

This device may substitute for the more expensive commercial counters and possesses certain advantages over them especially in being more versatile, since boxes can be added or more marbles used

Three Dimension Visualization of Blood Cells by Oblique Illumination The method described by Milton G Bohrod (Rochester Gen l Hosp) requires an oblique illumination device on the substage of the microscope

TECHNIC —The smear may be stained or unstained The appearance of the cells is somewhat cleared in stained smears Cover slip preparations are placed on a slide with the blood toward the objective The oil immersion objective is not used best results are secured with the high dry objective and a high power ocular The iris diaphragm is closed to almost its narrowest aperture and the condenser is lowered slightly The illumination is then caused to enter obliquely by adjusting the proper device Careful manipulation of the degree of obliquity and of the position of the condenser will afford an optimum point for visualization At this point the diaphragm may be opened slightly to increase illumination

The illusion of depth is increased by using a binocular attachment although a monocular microscope will give good results

Since the field so obtained is not of homogeneous illumination the method does not lend itself to direct photography for which the old method of superimposing the positive and negative film or plate and printing through them is still necessary

With oblique illumination the biconcave disk appearance in the normal blood smear is obvious The fulness of the megalocyte in pernicious anemia and the spherical nature of the cells in congenital hemolytic anemia are apparent The peculiar dimpled shape of the target cell is clearly seen Wider use of this method may disclose other peculiarities of blood cells of diagnostic importance

( ) Am J Clin Path 13 111 Jan ry 1943

Biopsy of Bone Marrow by a New and Simple Instrument Many hematologists rely chiefly on examination of material obtained by trephine but the minor surgical procedure involved with incision and resulting scar has precluded the general application of this method for diagnostic purposes Henry Turkel and Frank H Bethell[3] (Univ of Michigan) describe an instrument designed to obtain a small specimen of marrow with no more effort and less discomfort to the patient than are involved in ordinary aspiration With minor modifications the device can also secure biopsy material from tumors and soft tissues

INSTRUMENT —This consists of two needles with stylets—a 14 gage outer guiding needle and a 17 gage inner trephine needle The guiding needle is 2 3 cm long One end has a sharp beveled point and the other a hollow head with a slot into which the projection of the head of the stylet fits This keeps the point of the needle and of the stylet at the same cutting angle The guiding needle cuts through the skin and subcutaneous tissue without excising them and directs the trephine needle to the desired position

The trephine needle the diameter of which is equal to that of the stylet of the guiding needle is designed to slip within the guiding needle after the stylet is removed The length of the two needles may be varied but the relation must be such that the shaft of the internal needle is 5 mm longer than the entire length of the external needle The tip of the trephine needle has four saw teeth The inside surface of the tip is conshaped or convergent so that the tissue becomes wedged into the needle after being cut and remains there when it is removed The head of this needle is hollow but without a slot Its stylet has no projection on its head but its stem is slightly longer than the inner needle thus extending through the tip This additional length serves to express the biopsy material out of the needle and protects the cutting tip from injury when the inner needle is inserted into the outer one A standard adaptor or syringe would fit into the heads of both needle

TECHNIC —Under local anesthesia the outer needle with stylet in place is inserted until its point just engages the anterior lamella of the sternum the stylet is removed The inner needle with stylet in place is inserted into the outer

(3) J Lab & Clin Med 28 1461 1 July 1943

needle, the stylet is removed and the inner needle is turned back and forth through a half circle, while exerting slight pressure The cutting action is continued until the needle has entered the sternal cavity for 2 or 3 mm The needle is then revolved several times to insure detachment of the plug from the surrounding marrow

When it is desirable to prepare also films of aspirated marrow, the material obtained from the trephine hole is unsatisfactory because of admixture of excessive amounts of blood It is then preferable to anesthetize a sufficiently large area to permit insertion of an aspiration needle about 1 cm below the point of introduction of the trephine

For fixation, the authors use 100 cc Zenker's solution with 5 cc glacial acetic acid added just before using After 24 hours no further decalcification is required

Chemical Fractionation from Exudates of a Factor Promoting Leukocytosis is discussed by Valy Menkin and M A Kadish[4] (Harvard Univ) Earlier observations demonstrated a leukocytosis promoting factor in inflammatory exudates of various experimental animals and man Subsequent chemical studies showed this factor to be associated with the pseudoglobulin fraction of exudates The active globulin penetrates into the circulation from the inflammatory site and eventually induces a discharge of immature leukocytes from the bone marrow This active factor can be readily desiccated. In the dried form it maintains both its potency and its stability for many months The effect on the number of circulating leukocytes can be elicited by intravascular and to some extent by subcutaneous administration

Further studies indicated that preliminary removal of the euglobulin and albumin fractions from exudates will yield in the residual pseudoglobulins a more potent fraction usually free from any tendency to induce either local inflammation or the initial transitory leukopenic phase The level in the number of circulating leukocytes may increase 200 300 per cent within several hours Such potent fractions of the leukocytosis promoting factor induce marked hyperplasia of the bone marrow This

(4) Am J M Sc 05 363 368 March 1943

factor can also be conveniently dried by the in vacuo freezing method described by Mudd and his associates

Leukocytosis Induced by Methylacetamide with P Chloroxylenol is described by Bernhard Zondek and Yehuda M Bromberg (Rothschild Hadassah Univ) During investigations on the therapeutic use of halogenized phenols the solubility of p-chloroxylenol in various substances was studied Among these was methylacetamide which in contradistinction to other solvents induced a distinct leukocytosis in the blood stream when injected intramuscularly Methylacetamide alone produced a leukocytosis of short duration but when it was combined with p chloroxylenol the leukopoietic effect was prolonged and strengthened considerably P-chloroxylenol alone had no influence on leukopoiesis This leukocytosis is due especially to the granulated elements and becomes maximal 48 hours after injection

The effect of methylacetamide solutions with 25 per cent p chloroxylenol in leukopenic conditions was investigated in four cases of typhoid the only leukopenic condition at the authors disposal A boy 7 received 56 cc of the solution during five days which increased the leukocyte count from 5 000 to 12 000 the increase of neutrophils paralleling that of the leukocytes In another case that of a boy 10 the rather high dose of 72 cc given over five days induced a neutrophilic leukocytosis the count reaching a maximum of 32 400 on the fifth and sixth days after beginning of treatment The leukocyte count however dropped to initial levels 36 hours after stopping treatment

Further study revealed that this solution stimulated electively the granulopoietic function of the bone marrow not affecting the other elements of the white series erythropoiesis or thrombocytopoiesis The solution may thus be indicated in cases of agranulocytosis secondary to general infection

(5) Am J M Sc. 05 8 89 J u ry 1943

needle, the stylet is removed and the inner needle is turned back and forth through a half circle, while exerting light pressure The cutting action is continued until the needle has entered the sternal cavity for 2 or 3 mm The needle is then revolved several times to insure detachment of the plug from the surrounding marrow

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(4) Am J M Sc 05 363 64 M h 1943

Plasma Proteins (Albumin and Globulin) and Red Cell Volume Following a Single Severe Nonfatal Hemorrhage Robert Elman Carl E Lischer and Harriet Wolf Davey[7] (Washington Univ) made observations after hemorrhage in one series of experiments for 24 hours and in another series up to 7 days In the first group of 25 dogs 35 cc blood per kg body weight was removed and replaced with an equal volume of Ringer s solution Observations were made at 1 7 and 24 hours after hemorrhage The red cell volume fell rapidly one hour after hemorrhage and continued to do so during the entire period This was also true of the concentration of total protein during the first hour However there was a rise at 7 hours which was continued at 24 hours The relationship between albumin and globulin indicates that the fall in globulin was slightly less pronounced than that in albumin at the first hour but that the increase in the concentration of total protein at seven hours was due almost entirely to an increase in albumin fraction At 24 hours the changes in albumin and globulin were about the same indicating the beginning of globulin regeneration

In the second group 12 dogs were bled the same amount and observed for seven days In six of these Ringer s solution was used for replacement and in the remaining six a red cell suspension in Ringer s solution constituting a single plasmapheresis Figure 40 illustrates the changes occurring one week after hemorrhage The fall in red cell volume continued for 72 hours after which it was replaced by a slight rise at 7 days The albumin fraction on the contrary began to increase after the precipitate fall at 1 hour this increase was slowed at 72 hours and even at 7 days the original concentration of albumin fell short of being reached by about 10 per cent In contrast was the rapid return of globulin which reached its normal level between 24 and 72 hours continuing its increase

(7) Am J Phy 1 138 569 576 M 1 1943

[Pyogenic infection is an effective cause of leukocytosis in normal persons but not in patients with agranulocytosis It is possible but doubtful therefore that the agent here proposed will be effective in agranulocytosis —Eds]

Changes in Adhesiveness of Blood Platelets Following Parturition and Surgical Operations were studied by Helen Payling Wright[6] (London) to determine whether alterations in stickiness occur after such events when there are a rise in platelet count and a tendency for venous thrombosis to occur Serial observations on platelet count platelet stickiness (*on glass*) red cell sedimentation rate red cell count and hemoglobin percentage were made on 13 obstetric and 11 surgical patients a few hours before delivery or surgery, between *4 and 24 hours after and on the ensuing fourth* seventh tenth and fourteenth days

There was an increase in platelet stickiness and numbers in both groups of patients beginning on the fourth day and becoming maximal on the tenth day This increase in stickiness is probably due to rapid liberation of young platelets into the blood stream The red cell sedimentation rate [i e fibrinogen response —Ed] reached a maximum the fourth day and declined considerably by the tenth day In the obstetric group red cell sedimentation rate was above normal before delivery average corrected figure being 23 mm per hour It reached 27 mm per hour on the fourth day In the surgical group it reached a peak of 21 mm per hour the fourth postoperative day and returned to the initial rate the twenty first day The red cell count and hemoglobin percentage in both groups were below normal but the degree of anemia was slight It is concluded that factors influencing the stickiness of the platelets are not the same as those affecting the agglutinability of the red cells

[The degree of rouleaux formation is the chief variable in sedimentation rates The red blood cells are not agglutinated in the usual sense of the word —Eds]

(6) J P th & Bact 4 181-188 Oct be 194

globulin showed a similar effect i e its rise was less pronounced than in the other six animals After 24 hours however the changes in the albumin and globulin were similar in the two groups

In the third group of eight dogs no fluid was used for replacement and the amount of blood removed was somewhat larger Nevertheless the fall in the hematocrit value *as well as in the albumin and globulin concentration* was quite similar The changes within the first hour however were more gradual

These and other findings justify a biochemical approach to the problem of shock following hemorrhage Using the term compensation to imply recovery from the effects of severe hemorrhage it may be said that a hemorrhage is compensated when hemodilution is sufficient to restore and maintain blood volume adequately to support the circulation Hemodilution is insufficient in maintaining blood volume only because of the low protein content of the diluting fluid

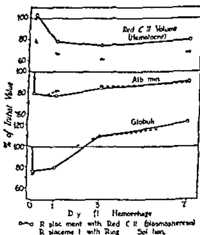
The protein content of the fluid which restores blood volume is significant because it contributes the colloidal osmotic pressure of the blood on which circulation and fluid interchange depend The fact that the diluting fluid becomes poor in albumin is significant because albumin is responsible for 85 per cent of the blood s colloidal osmotic pressure

The *defect in the compensatory mechanisms would* seem therefore to lie in the inability of the body to correct the hypo albuminemia induced by the hemorrhage In other words fatalities following severe blood loss *are due to inability of the body to restore blood* volume with fluid containing sufficient albumin This biochemical approach to the problem of shock in hemorrhage emphasizes the acute protein deficiency and suggests the need for means to increase the output of albumin by the liver to obviate the necessity of supplying exogenous protein

A Study of the Splenic Venous Blood obtained at the

so that at the end of 1 week it had exceeded the orig inal concentration by approximately 15 per cent

Of interest are the findings in the experiments in which plasmapheresis was carried out The one hour specimen showed no fall in hematocrit value because of red cell replacement (Fig 40) Nevertheless in 24 hours the hematocrit value dropped more rapidly than in the animals in which replacement was with Ringer



F 40—Rel t ship du ng o e w ek B th se es of cu ves were p otted from averag v lu bta ned n bl din expe me ts P ounced fall n d ll vol m t 4 hou s is c nt nued mo l wly at 7 hours and replaced b sl ght se at 7 days Aft 4 h u n t el t ely low re ener t on f lbumin comp d wth ap d gene at on of glo u n g neral s mil ty n u when pl m phe es was d n

solution From this point on the red cell volume curve paralleled exactly the curve in the latter experiments The steeper fall in red cell volume between the first and 24 hour periods is obviously due to a greater hemo dilution and explains the difference in the behavior of the albumin and globulin fractions during this period as compared with that when Ringer s solution alone was used Thus the albumin fell after plasmapheresis in contrast to the rise in the experiments in which Ringer s solution alone was used The change in the

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A Study of the Splenic Venous Blood obtained at the

time of splenectomy for various diseases is presented by Cecil James Watson and John Randolph Paine[8] (Univ of Minnesota) In many instances a marked increase in erythrocyte concentration occurs after injection of adrenalin into the splenic artery This increase is associated with a decrease in mean corpuscular hemoglobin concentration and also with an increase in fragility and spheroidicity The exact cause of the decrease in hemoglobin concentration is unknown It may be due to an intracorpuscular degradation of a *fraction of the hemoglobin in the intact erythrocytes* during their sequestration in the splenic pulp and sinuses Since the mean corpuscular volume was not significantly increased this effect was not attributable to the imbibition of fluid by the cells

Surgery of the Spleen in Blood Dyscrasias E L Eliason and L W Stevens[9] (Univ of Pennsylvania) reviews the literature of the last 10 years and compiles a statistical report showing mortality and life expectancy following splenectomy in cases of splenic anemia thrombocytopenic purpura and ictero anemia A similar report on 63 personal cases is made Fairly good results were obtained in splenic anemia thrombocytopenic purpura and hemolytic ictero anemia, but the field was broadened disastrously when pernicious anemia leukemia aplastic anemia toxic infections allergies drug anemias etc were included

In the authors series of 28 patients with splenic anemia treated by splenectomy mortality was 25 per cent Twenty eight per cent of the survivors lived 5 years and 21 per cent 10 years Seven of the eight patients who died had extensive liver damage In this disease splenectomy gives the patient the best chance The earlier operation is done the lower will be surgical mortality and the greater life expectancy One of the authors (E L E) believes that splenectomy is the only choice even with cirrhosis Operative mortality

(8) Am J M S 205 493 501 Ap 1 1943
(9) b g y 13 177 187 F b u y 1943

should not exceed 10 per cent and some patients have lived 20 years

Essential purpura may be divided into four groups In those cases with mild or moderate bleeding in the initial attack conservatism and possibly transfusions will result in a high percentage of permanent cures When mild bleeding occurs with recurrent attacks splenectomy is definitely indicated if conservative treatment fails The fulminating type in the initial attack presents the most difficult problem It is difficult to evaluate the results that have been reported owing to lack of data It is not unlikely however that the high mortality has been due to delayed splenectomy and insufficient postoperative care In the group characterized by severe bleeding in recurring attacks those patients who have survived by reason of remissions should be treated by transfusions as long as they improve If improvement ceases splenectomy is indicated at once

Results following removal of the spleen for purpura haemorrhagica have been so satisfactory that when the disease is an inconvenience and does not respond to nonoperative treatment splenectomy should be advised Elimination of infection is important in prevention of recurrent purpura Recurrence of a serious nature after splenectomy is unusual

The congenital type of hemolytic ictero anemia (hemolytic jaundice) appears in infants and children [and sometimes is unrecognized in adults —Eds] The acquired form usually appears after age 20 and is often more severe Splenectomy is the treatment of choice in true congenital ictero anemia Permanent cure is obtained It is essential that diagnosis be correct since benefit is not obtained in atypical cases It is wiser to operate during a remission unless a rapid uncontrolled acute phase makes immediate surgery imperative In the adult form splenectomy is not always indicated especially if the disease is mild

TRANSFUSIONS OF BLOOD AND BLOOD SUBSTITUTES

Treatment of civilian and military casualties of war, including burns hemorrhage and traumatic shock has greatly stimulated interest in various types of stored blood plasma and plasma substitutes This section is devoted to contributions concerning the use of these agents —Eds

Practical Considerations in the Therapeutic Use of Blood Derivatives are reviewed by L R Newhouser and L L Lozner[1] (U S Naval Med School)

Certain misconceptions concerning use of serum albumin have arisen Albumin should not be considered a substitute for plasma or whole blood It represents a relatively stable concentrated solution of that fraction of the plasma proteins mainly responsible for maintenance of the colloid osmotic pressure of the blood. The chief dangers in the use of human serum albumin arise from the facts that it represents but one of the serum proteins and that it is extremely hypertonic and supplies practically none of the fluid that may be needed in treatment of traumatic shock burns or hemorrhage In burns use of citrated plasma should follow use of albumin as soon as possible In traumatic shock albumin must be considered solely an emergency first aid measure The precautions relative to increasing hemorrhage aggravating existing dehydration increasing apparent anemia potential pulmonary edema the limit of dosage and the stability of the solution must be constantly borne in mind If it is desired to administer a hypertonic blood derivative as in hypoproteinemia or in certain burned patients concentrated plasma may be preferable to albumin The concentrated solution of human serum albumin is quite stable at the moderate temperatures in the temperate zone

Plasma when prepared by a closed method with scrupulously aseptic technic may be preserved in the

(1) N w England J Med 8 6 1 674 May 7 1943

liquid state at room temperature in the temperate zone for at least 14 months The permissible temperature range of preservation probably lies between 15 and 30 C Below this range excessive fibrin precipitation may occur and above it protein denaturation occurs rapidly Although a small amount of fibrin precipitation is almost inevitable when plasma is preserved in the liquid state this does not affect its efficacy or safety It is imperative however that a filter be used in the intravenous set when plasma is administered

Frozen plasma may be preserved indefinitely if stored below —15 C without loss of any of the ther molabile constituents such as prothrombin complement and antihemorrhagic factor (plasma thromboplas tin) Thawing must be done in a *water bath* at body temperature (37 C) with occasional shaking and should not take longer than 30 minutes per bottle of plasma A filter is not absolutely necessary if the frozen plasma is thawed properly maintained at room temperature and administered within two to three weeks after thawing However inclusion of the filter in the intravenous set is an excellent safeguard

If accidental thawing occurs the plasma may be re frozen immediately or thawing may be allowed to con tinue at 37 C and plasma stored as liquid plasma from that time on or it may then be refrozen In any event much of the prothrombin and complement will be lost and a filter must be used in the administration set

The standard Army Navy package of dried plasma can survive a wider range of temperature variation without denaturing or precipitating protein than can any of the other blood derivatives or forms of preser vation The package should not be permitted to freeze and should not remain for any length of time above 55 C Care must be taken to be certain that at the time of restoration the water temperature is not above 37 C for in this event the proteins may be either de natured or precipitated and untoward reactions may

ensue The solubility time should be less than three minutes with a small amount of shaking, and the gross appearance should be that of an opalescent or turbid solution without gross sediment precipitate or gel formation

Following a severe injury or burn 500 1 000 cc plasma or 25 50 Gm albumin is an advisable initial dose An attempt should be made to utilize the laboratory aids of red cell count hemoglobin level hematocrit reading and total protein content for regulation of subsequent dosage but the medical officer will frequently have to rely solely on clinical response and pulse and blood pressure readings In burns a rough but useful rule for estimating the first day s dosage is *to administer 100 cc plasma for each 1 per cent of the* body surface burned up to a maximum of 4 000 to 5 000 cc The *knowledge that the palmar surface* of one hand represents approximately 1 per cent of the total body surface is often useful When hemoconcentration has *supervened it has been advised that 100 cc* plasma be given for every point the hematocrit reading is above 45

Use of whole blood transfusions supplementing plasma or albumin may be significant in determining *prognosis of a wounded patient The need* for red cells may be masked initially by hemoconcentration In burns moderate anemia is prone to develop and is affected apparently only by blood transfusions

Rate of administration of these derivatives *should not exceed 10 cc per minute for plasma or 5 cc per* minute for albumin unless clinical shock is present in which event it may be advisable to administer *the* material with double this speed

[Many other useful technical details are given in the original article —Eds]

Red Cell Suspension Transfusions Leslie Watson (Univ of Leeds) administered 46 transfusions of *red* cell suspensions to 23 patients 18 were administered

( ) Lancet 1 107 111 Jan 23 1943

to outpatients who returned home a few hours later To obtain plasma human blood is procured from the blood bank and the plasma is removed the remaining blood cells forming a by product which is normally discarded

The red cell suspensions were prepared from stored blood of group O Blood was drawn from the donor into a bottle containing sodium citrate solution each bottle finally containing about 100 ml of 3 per cent sodium citrate solution and 440 ml blood The mixture was then stored at 4 C and after about 7 days (the actual period varied from 3 to 12 days depending on the local demand for blood and plasma) the supernatant plasma was drawn off The remaining mass was filtered through a gas mantle and the red cells from several bottles were bulked and stored at 4 C until required The time elapsing between removal of the blood from the refrigerator for processing and return of the red cell suspension for storage was under 2 hours the suspensions were stored for 1 48 hours before transfusion

A bottle of red cell suspension would contain about 290 ml packed red cells 157 ml plasma and 75 ml citrate solution this would furnish a suspension containing about 18 Gm hemoglobin per 100 ml suspension

Red cell suspension transfusions were found to be a satisfactory substitute for whole blood transfusions when the objective is to increase the oxygen carrying capacity of the blood These transfusions are especially valuable when a maximum rise in hemoglobin with a minimum volume is desired When large volume group O transfusions are administered to patients of other than group O use of the suspension reduces the risk of a reaction due to transfusion of large quantities of iso agglutinin in group O plasma A simple method of calculating transfusion volume is suggested which is especially valuable in transfusions for the young

If the pretransfusion hemoglobin, body weight of the recipient and desired rise of hemoglobin are known, the transfusion volume can be accurately prescribed, e g initial hemoglobin 5 Gm per 100 ml body weight 55 Kg desired hemoglobin after transfusion 15 Gm per 100 ml hemoglobin concentration of red cell suspension 20 Gm per 100 ml Then blood volume is approximately 55/11 = 5 L Total hemoglobin in the body before transfusion is 5 000 × 5/100 = 250 Gm, that in the body after transfusion 5 000 × 15/100 = 750 Gm Therefore the amount of hemoglobin to be added is 750 — 250 = 500 Gm Five hundred Gm hemoglobin is contained in 2 500 ml suspension

Red Cell Transfusions in Treatment of Anemia Howard L Alt[3] (Northwestern Univ) states that the main value of red cell transfusions is to increase the erythrocyte count in patients with anemia After severe hemorrhage spontaneous recovery of the anemia takes six weeks or longer In such a case daily administration of red cells from a liter of blood will bring the erythrocyte count to normal within a few days If cells could be made available to the armed forces it would materially hasten rehabilitation of wounded men who have suffered from hemorrhage In patients with severe iron deficiency the hemoglobin value can be raised rapidly with red cell transfusions During the gradual destruction of the transfused cells iron is released for further hemoglobin formation Red cell transfusions are also effective in other types of anemia Their use in progressive refractory anemia has already been emphasized

The chief advantage of transfusions with red cell suspensions over whole blood is the factor of economy With widespread use of plasma great quantities of red cells will continue to be a by product Should red cell tranfusions come into common use it will be possible to divide the cost of whole blood between the

(3) J A M A 122 417-419 June 1 1943

plasma and the cells If and when red cell suspensions become generally available at a low cost it is rational that they should be used in larger amounts and more frequently in treatment of anemia than whole blood is used at present

[Red cell transfusions ar of course *not* a substitute for whole blood or pla ma in shock where increase in plasma volume is the immed ate objective —Eds]

Investigation of Hemolytic Transfusion Reactions *According to* P L Mollison[4] *diagnosis of a hemolytic* reaction is based on evidence of increased blood de struction following transfusion and on demonstration of a cause for this destruction When considerable in travascular hemolysis occurs part of the hemoglobin is broken down liberating hematin This combines with serum albumin to form methemalbumin When the con centration of hemoglobin in the plasma exceeds ap proximately 135 180 mg per 100 cc some hemoglobin is excreted by the kidney Some degree of renal in sufficiency may occur due to blockage of the renal tubules with acid hematin Extravascular destruction of red cells results in production of bilirubin Apart from such signs of increased destruction the recipient may evince constitutional disturbance although oc casionally a hemolytic transfusion reaction may occur without giving rise to symptoms

The commonest causes of severe hemolytic trans fusion reactions are (1) mistakes in blood grouping (2) use of Rh positive blood for transfusion to re cipients sensitized to the Rh agglutinogen and (3) fail ure to maintain adequate standards in blood storage *Incompatible red cells may be either agglutinated or* hemolyzed by the recipient s plasma in vitro It is im portant to realize that even when only agglutination occurs in vitro intravascular hemolysis may occur in vivo When Rh positive blood is transfused to a re cipient whose serum contains anti Rh agglutinins se vere intravascular hemolysis may follow although

(4) B t M J 1 5 953 M y 1 9 61 M y 8 1943

hemolysis never occurs in vitro when Rh positive cells are incubated with serums containing anti Rh antibodies Clumps of agglutinated donor cells may be found in blood samples withdrawn from the recipient. There is usually an initial reduction in agglutinin titer lasting for one to two days after transfusion probably due to absorption by the incompatible erythrocytes Then there is a rapid increase, usually reaching a peak 10 20 days after transfusion

Rate of destruction of erythrocytes of stored blood in the circulation of a normal recipient after transfusion depends mainly on length of storage preservative solution used and temperature of storage Erythrocytes of blood stored in a simple solution of sodium citrate survive far less well in the recipient s circulation than the erythrocytes of blood stored in a solution to which glucose has been added Blood that is left standing at room temperature before transfusion may give rise to signs of blood destruction when it is transfused Blood may become hemolyzed by the action of contaminating organisms by being overheated or by being stored for excessive periods under unsuitable conditions

Investigation of hemolytic transfusion reactions is facilitated if a sample of donor blood and a pretransfusion sample from the recipient are kept available for testing for at least 24 hours after transfusion [editors italics] When the patient is seen within 24 hours after a transfusion and a hemolytic reaction is suspected a large sterile venous blood sample and a clean urine sample should be obtained

In an obscure case most of the following tests may be necessary (1) donor s blood—determination of amount of free hemoglobin of grouping (both cells and plasma) and of Rh group testing of cells against recipient s pretransfusion serum and estimation of agglutinin titer in plasma (2) recipient's blood (post transfusion sample)—bacteriologic examination determina

tion of amount of hemoglobin bilirubin and methemalbumin (examination of pretransfusion sample serves as control) examination of suspension of cells for presence of agglutinates group determinations Rh group determination and examination for presence of anti Rh agglutinins titration of agglutinins in the serum for comparison with results of titrations on samples obtained later and on pretransfusion sample and differential agglutination tests (if necessary), (3) recipient s urine—oxyhemoglobin and methemoglobin determinations examination of sediment for pigment casts and urobilin determination

Not all these tests will have to be applied in most cases The most likely cause is tested for first then other tests are applied only if the first ones are negative or inconclusive For example preliminary regrouping of the blood of donor and recipient may reveal a mistake in A B O grouping In such cases no other tests will be necessary When a blood sample is taken from the recipient immediately after an incompatible transfusion it may contain an appreciable number of donor cells and this may lead to a mistaken diagnosis of the recipient s group In the case of incompatibility due to Rh differences mistakes are more apt to occur however When an Rh negative person already sensitized to the Rh agglutinogen is transfused with Rh positive cells the post transfusion sample may contain appreciable numbers of Rh positive cells although their destruction is proceeding rapidly This may lead to the impression that the recipient is Rh positive Use of powerful serums should enable this appearance of partial agglutination to be recognized with certainty from that of complete agglutination

When no other cause can be found the possibility that the signs of hemolysis are due to destruction of the recipient s own red cells by high titer incompatible agglutinins in the recipient s plasma should be considered In such a case application of the method of differential

hemolysis never occurs in vitro when Rh positive cells are incubated with serums containing anti Rh anti bodies Clumps of agglutinated donor cells may be found in blood samples withdrawn from the recipient There is usually an initial reduction in agglutinin titer lasting for one to two days after transfusion probably due to absorption by the incompatible erythrocytes Then there is a rapid increase usually reaching a peak 10 20 days after transfusion

Rate of destruction of erythrocytes of stored blood in the circulation of a normal recipient after transfusion depends mainly on length of storage preservative solution used and temperature of storage Erythrocytes of blood stored in a simple solution of sodium citrate survive far less well in the recipient s circulation than the erythrocytes of blood stored in a solution to which glucose has been added Blood that is left standing at room temperature before transfusion may give rise to signs of blood destruction when it is transfused Blood may become hemolyzed by the action of contaminating organisms, by being overheated or by being stored for excessive periods under unsuitable conditions

Investigation of hemolytic transfusion reactions is facilitated if a sample of donor blood and a pretransfusion sample from the recipient are kept available for testing for at least 24 hours after transfusion [editors' italics] When the patient is seen within 24 hours after a transfusion and a hemolytic reaction is suspected a large sterile venous blood sample and a clean urine sample should be obtained

In an obscure case most of the following tests may be necessary (1) donor s blood—determination of amount of free hemoglobin of grouping (both cells and plasma) and of Rh group testing of cells against recipient s pretransfusion serum and estimation of agglutinin titer in plasma (2) recipient's blood (post transfusion sample)—bacteriologic examination determina

an Rh positive fetus at a later pregnancy Women who may require transfusion during or after pregnancy should be typed for the Rh factor and if Rh negative receive only similar blood This is especially important if the obstetric history suggests the birth of an infant with erythroblastosis foetalis In the latter event the husband is a dangerous donor

The modified compatibility test of Levine (incubation of the mixture of the patient s cells and donor s serum) occasionally reveals the presence of the anti Rh agglutinin in the recipient s serum If it is negative however it is not a guarantee that a hemolytic reaction will not occur

Rh negative donors should be listed and be available for transfusion of Rh negative patients or those untyped recipients whose history suggests the possibility of transfusion reactions

The Inhibitory Effect of Human Serum on the Iso Agglutination of Red Cells is discussed by Herbert H Lubinski[6] (Montreal) It is generally agreed that transfusion of type O blood and intravenous injection of pooled serum or plasma can be done without regard to blood type despite the presence of agglutinins and hemolysins specifically effective for the recipient s red cells It is presumed that the injected serum is highly diluted or that agglutinins and hemolysins of the injected O serum are absorbed and neutralized by the type specific substances (agglutinogens) present in the recipient s tissues and serum Levinson and Cronheim demonstrated quantitatively the neutralization of agglutinins by antagonistic serum They showed that the use of A serum as a diluent in titration of B serum and vice versa reduces the titer of agglutination as compared with the titration when saline solution is used They appear to consider the reduction of agglutination as due to the group specific substances in serum

Lubinski attempted to confirm the findings of Levin

(6) J Immu l 44 95 100 Ju 194

agglutination is practically essential in establishing that the signs are not due to destruction of the donor cells although the agglutinins in the donor's plasma must also be titrated

Hemolytic Transfusion Reactions Due to the Rh Factor A Preventable Danger Louis K Diamond[5] (Harvard Univ) reviews 10 cases of hemolytic transfusion reactions In every case the recipient received compatible blood according to grouping and cross matching by the ordinary methods Later investigation disclosed that the incompatibility involved the Rh factor Each recipient was Rh negative and through the development of iso immune bodies to the Rh factor suffered a hemolytic reaction when Rh positive blood was administered *Following the hemolytic reaction use of Rh negative blood for subsequent transfusions in each patient resulted in no further difficulties* [editors italics]

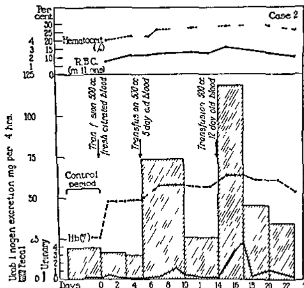
Iso immunization occurred in some patients as the result of previous transfusions with Rh positive blood in others as the result of a pregnancy involving a fetus having Rh positive blood cells In still another patient an anti Rh agglutinin of natural origin seemed to be present Mixtures of recipient s Rh negative cells and donor s Rh positive cells were observed in the blood of three patients shortly after hemolytic transfusion reactions had occurred This necessitated care in interpretation of the test for Rh positive cell agglutination

In two cases women of child bearing age developed iso immunization to the Rh factor through use of Rh positive blood for transfusions and in both these cases this seemed to have been the direct cause of the birth of an infant with severe erythroblastosis foetalis in a subsequent pregnancy Patients who are likely to have repeated transfusions should be typed for the Rh factor to avoid immunizing Rh negative persons by use of Rh positive blood This is especially important in women of child bearing age to avoid the possibility of harming

(5) New Engl nd J M d 7 857 86 D 8 194

but preliminary studies indicate that combination of antibody and antigen does not remove cutaneous re acting properties of the antigen Although plasma was used in this study there is no reason to believe that serum would yield different results

Quantitative Urobilinogen Excretion Following Transfusions of Stored and Fresh Blood Louis R Wasserman Mario Volterra and Nathan Rosenthal[8] (Mount



F g 41 —P o r e e n bil n g n t n w th e in t g tim of b k bl d

Sinai Hosp New York City) used the measure of uro bilinogen excretion to determine duration of viability of transfused blood cells Three patients with aplastic anemia were selected for study because this disease ex hibits a fairly constant rate of hemolysis i e an ap proximately constant excretion of urobilinogen Repeat

(8) Am J M S 04 356 364 S pt mbe 1942

son and Cronheim He found that when a hemagglutinating serum is diluted with an antagonistic or previously absorbed hemagglutinating serum instead of with saline solution the titer of agglutination is reduced, in some cases to zero Since this result can be achieved by any human serum freed of agglutinins and by serums of the same type and by O serum it therefore cannot be considered as caused by the type specific substances but by an unspecific factor found in different degree in any human serum Heating to 56 C for one half hour does not affect this factor

A and B Substances as Cause of Reactions Following Human Plasma Transfusions *Milton Levine and David State*[7] (Univ of Minnesota) believe that clinicians tend *to regard plasma as innocuous because evidence for* plasma reactions has not been presented Their experience has been that cutaneous reactions to one or more plasmas of different blood groups occur in about 20 per cent of individuals tested *These tests correlate with* occurrence of reactions following administration of group specific plasmas due to A and B substances

Clinical evidence presented shows that A and B substances in plasma and purified combined A and B substances may cause reactions after intravenous administration in sensitive persons This sensitivity is not associated with any particular group in recipient or donor it occurs when the recipient has the antibody corresponding to the administered antigen but not every person having the antibody will react to the transfused antigen The authors have had patients of all blood groups who showed no sensitivity by either cutaneous test or intravenous administration

No reactions followed intravenous administration of plasma in patients with negative cutaneous tests Absence of reactions when cutaneous tests are negative suggests the regular use of these tests especially when using unpooled plasma Results of pooling are unknown

(7) J A M A 1 0 75 7 Sept 26 194

Both mixtures were isotonic with normal plasma Blood can be stored in these solutions up to six weeks or two months at 4 C with less than 1 per cent hemolysis The buffered solution gives slightly better cell preservation during storage and favors less dense packing of cells on sedimentation

Survival of erythrocytes after transfusion was followed in 52 mental subjects by the MN (agglutination) method of Wiener Specimens stored up to two months were used without any reaction The buffered mixture did not exhibit special merit Results of the study indicate that cells stored up to 18 days by either method survive as well as fresh cells after transfusion Even with 25 to 30 day old blood cell survival after transfusion is sufficiently high during the first three weeks to warrant use of such specimens in treatment of severe blood loss when fresher blood is not available

There is evidence that some of the transfused cells may be stored instead of being destroyed and that they are released into the circulation again between the fifteenth and the twenty fifth day A second and less marked rise in donor cell count often is observed about the sixtieth day

Survival after Transfusion of Human Erythrocytes That Have Been Stored in Citrate Glucose is reported by William P Bell and Florence Rosenstein[1] (Philadelphia)

METHOD—Blood was collected in 20 per cent dihydric sodium citrate to make a final concentration of 0 4 per cent, and glucose 5 4 per cent in water was added in quantity equal to half the volume of blood Flasks were kept undisturbed at 4 to 6 C *The life span of erythrocytes after entering recipient s circulation was determined by modification of* Ashby s method of nonagglutinable cell counts

Results of this and previous studies indicate that chilled citrated human blood undergoes rapid deterioration in all of its cellular and some of its plasma components When such blood is administered to patients the

(1) Am J M S 04 504 507 Oct b 194

ed transfusions of blood containing citrate or glucose and citrate of ages varying from a few hours to 18 days were given the urobilinogen excretion in urine and feces being determined before and after each transfusion by Watson's modification of Terwen's method

The results in a woman 70 are presented here

Hemoglobin was 26 per cent Average daily excretion of urobilinogen was 19 5 mg per 24 hours in the feces and 0 21 mg in the urine The case was followed 25 days A 500 cc transfusion of fresh citrated blood induced no rise in pigment excretion in one week In three days after transfusion of 500 cc of 5 day old citrated blood, fecal urobilinogen rose from 14 8 to 74 mg per 24 hours and in seven days dropped to pretransfusion level Blood stored 12 days caused a rise to almost six times the pretransfusion level (118 mg per 24 hours) *within 3 days with gradual fall to original level* in a week Transfusion of fresh blood was followed by a greater rise in hemoglobin and red cells Increase in urobilinogen excretion was directly proportional to age of the blood transfused (Fig 41)

The authors conclude that in anemias use of blood stored for more than seven days is inadvisable In the three cases fresh blood caused little or no increase in pigment excretion during the first week following transfusion As blood stored for varying periods of time was given greater quantities of urobilinogen were excreted almost immediately and usually continued over a longer period Addition of glucose to the preserving solution prolonged retention and utilization of transfused blood in agreement with many studies particularly those of DeGowin and his co workers Plasma itself when transfused caused no increase in excretion of urobilinogen

Survival of Preserved Erythrocytes after Transfusion O F Denstedt Dorothy E Osborne H Stansfield and I Rochlin[9] (McGill Univ) conducted an investigation to determine the merits of two blood preservative mixtures the one an unbuffered citrate dextrose solution and the other buffered with phosphate at pH 7 4

(9) C ad M A J 48 4 486 Jun 1943

Spirochetal Survival in Frozen Plasma Because of the possibility that blood from syphilitic donors treated or not, might be used for the preparation of plasma and to avert loss of possible donors or of blood already drawn which is found to have a positive serologic reaction and avoid the labor of making such determinations on blood collected for plasma Mark M Ravitch and John W Chambers[2] (Johns Hopkins Univ) experimented to determine the survival of spirochetes in frozen plasma Human and rabbit plasma heavily inoculated with Treponema pallidum and frozen at —20 C for 48 hours or longer was not infectious for normal rabbits but was infectious when the freezing period was only 24 hours Under these conditions the incubation period was prolonged even though the experimental animals received an inoculation dose twice the size of that given the controls

Jaundice Occurring One to Four Months after Transfusion of Blood or Plasma Paul B Beeson[3] (Emory Univ) reports seven such cases and suggests that the jaundice was probably caused by the transfusions

A number of instances are recorded in which inoculation of groups of people with human plasma serum or lymph has resulted in outbreaks of an illness resembling catarrhal jaundice A distinctive feature of these cases has been a long incubation period of 4 to 30 weeks—in most cases 8 18 weeks The first large outbreak occurred in 1883 1884 among shipyard workers vaccinated with human lymph from patients with vaccinia One to seven months later 191 of 1 289 persons became jaundiced while 500 other workers in the same shipyard vaccinated with a different lot of lymph were unaffected In England 41 cases of jaundice occurred among 109 children who had been inoculated with measles convalescent serum Yellow fever vaccination using vaccines containing human serum has been the cause of several out

(2) Bull Joh H pk ns Hosp 71 99 303 N vemb 194

(3) J A M A 121 133 1834 Ap 4 1943

red cells survive as long as those of fresh blood provided storage has not exceeded two or three days With each additional day of storage, however they are progressively less useful to the patient and after seven days of storage are apparently treated by the human organism as foreign bodies and eliminated in 24 to 48 hours Addition of glucose to citrated blood enhances its keeping properties about four times (Fig 42) Glucose treated

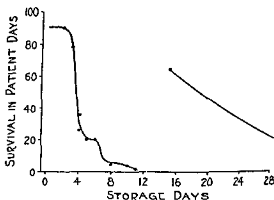


Fig 42 —R lat n between sto g t me and survival of eryth o ytes after transfus on Observat on n left of chart f t c t ated blood th se on ght to blood st ed in citrate glucose

cells stored 26 days had not reached the 'foreign body state characteristic of citrated cells after 7 or 8 days of storage Moreover erythrocytes of blood to which glucose has been added will after 14 days storage be detectable in the recipient s blood stream (where they presumably function) for about 50 days This survival is comparable to that of citrated cells stored three or four days It is not however as long as survival of fresh unstored cells The clotting properties of stored blood diminish so rapidly that it seems wise to use only fresh blood in transfusions for those with hemorrhagic diathesis In treatment of sepsis a storage limit of five days is advisable

Four of these seven patients received four or more transfusions involving relatively large volumes of blood or plasma This is probably significant only to the extent that the risk of receiving a jaundice producing substance in a transfusion may be increased in proportion to the number of donors from whom blood or plasma is received Volume alone does not seem important since the volume of human serum or plasma which caused the postvaccination cases was small It has not been possible to trace the donors in these cases However in some previous outbreaks the donors have been traced and have not presented any evidence of illness subsequent to the time at which they gave blood

The present large scale use of blood and plasma transfusion may lead to the occurrence of a considerable number of such cases of hepatitis It seems highly probable that they may be occurring not infrequently but are not being recognized If one were unaware of the fact that jaundice may follow inoculation with homologous serum or plasma after a long latent period one would be unlikely to attach any significance to a history of transfusion three months previous to onset of a patient s illness The real frequency of this complication of transfusion will be known only when there has been concerted effort to recognize such cases

Two practical measures are indicated A careful record should be kept of the source of blood or plasma administered to each patient and a small portion of blood or plasma should be set aside at the time of transfusion so that in the event of subsequent cases of hepatitis some of the causative material will be available for study

[Clinical reports by pra t t oners who are aware of this probab l ty can be of value in adding much needed information —Eds]

Effect of Iron on the Hemoglobin Regeneration in Blood Donors Data presented by Adelaide P Barer and Willi M Fowler[4] (State Univ of Iowa) indicate that administration of iron to blood donors hastens re

(4) Am J M S 0 9 16 J n 1943

breaks of hepatitis including those among American soldiers Evidence has pointed to the human serum in the vaccines as the source of jaundice in each of these outbreaks consequently, the vaccines now being used are made without human serum A recent memorandum by the British Ministry of Health describes an outbreak of jaundice involving 86 of 266 soldiers inoculated with convalescent plasma from mumps patients Also reported are 12 cases of jaundice from several sources in persons previously given transfusions of plasma or of whole blood

The clinical features of these illnesses have resembled to some extent those of common infective hepatitis or catarrhal jaundice Certain manifestations however have been noted in the homologous serum cases which may assist clinical differentiation Urticaria and various types of erythema are described For example skin rashes were noted in 41 7 per cent of the mumps plasma cases Also a transient generalized arthritis has been an early manifestation in some instances In most cases the symptoms were mild but some of the affected *persons were severely ill and deaths occurred* The cause of these diseases has not been established A favored explanation is that the jaundice is caused by a virus which happened to be present in the body fluids of the donors and which after a long incubation period produced a hepatitis in the recipient Another suggestion is that this disease is the result of an immune mechanism in which following inoculation with homologous blood or plasma an individual develops antibodies which cause injury to his own tissues

In the seven cases reported by Beeson a clinical diagnosis of acute catarrhal jaundice was made in six and toxic hepatitis' in the seventh No patient was severely ill A point of interest is the fact that skin eruption and joint pains were the initial symptoms in one case while in another the initial symptom was generalized urticaria These observations correspond with previous ones

hemolysis than the fecal content of urobilinogen alone When the mass of circulating hemoglobin is diminished the absolute content of urobilinogen in the feces may be normal or low, even though hemolysis is increased Under such circumstances a hemolytic index may be expressed by the following equation

$$\frac{\text{average (of 4 days) daily output of fecal urobilinogen (mg)} \times 100}{\text{total hemoglobin} \left(\text{hemoglobin [Gm./100]} \times \frac{\text{total blood volume}}{100}\right)}$$

This index furnishes information regarding the amount of excreted urobilinogen derived daily from 100 Gm circulating hemoglobin Because an individual s daily output of fecal urobilinogen is irregular the minimal period for estimation of a fairly good daily average is four days With diarrhea constipation or fever even this computation may be grossly inaccurate The authors used the Gibson Evans dye method for estimating blood volume a more accurate method than previous dye methods since the blue dye can be read accurately in the photo electric colorimeter even with slight hemolysis

The hemolytic index used in the study and evaluation of hemolytic syndromes varied in eight normal adults from 11 1 to 20 8 indicating that at least 11 1 mg urobilinogen is normally derived from 100 Gm hemoglobin Conditions in which a lowered hemolytic index was found included iron-deficiency anemia polycythemia and the postsplenectomy state Increased hemolytic indexes were found in pernicious hemolytic and Cooley s anemia and Gaucher s disease The hemolytic index permits a better evaluation of pigment metabolism than does simply the absolute value of the daily excretion of urobilinogen Knowledge of the index permits expression of any given urobilinogen excretion in percentage of the expected minimal or maximal values which is of definite value in interpreting the output of pigment in various blood disorders

Survival of Normal Erythrocytes after Transfusion to Patients with Familial Hemolytic Anemia (Acholuric Jaundice) J V Dacie and P L Mollison[6] (S W Lon

generation of hemoglobin and shortens the recovery period If the drug is given continuously, and repeated blood donations are given the effect of iron becomes less marked during the second recovery period and has no effect on the rate of hemoglobin regeneration during subsequent recovery periods In most individuals who give many donations while on continuous iron therapy there is a secondary and late increase in hemoglobin regeneration after five to six donations but this is usually not as great as the first response that was obtained On the whole there is a gradually decreasing effect from iron therapy

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HEMOLYTIC ANEMIAS

Interest in the so called hemolytic anemias continues to be evinced as indicated by the articles in this section —Eds

***Use of Daily Fecal Output of Urobilinogen* and Hemolytic Index in Measurement of Hemolysis** Edward B Miller Karl Singer and William Dameshek[5] (Boston Dispensary) state that the daily amount of urobilinogen excreted in the feces shows great fluctuation (50 200 mg) due partly to the complicated endogenous metabolism of urobilinogen and partly to variations in intestinal motility There are furthermore marked individual differences dependent chiefly on the total mass of circulating hemoglobin This last named value is obtained from the concentration of hemoglobin in grams per cent and from the total blood volume The latter varies directly as does the basal metabolic rate with the subject s surface area Thus to some extent at least the daily output of urobilinogen in the feces is an expression of the surface area which must be taken into account in its evaluation Since the only source of fecal urobilinogen is the hemoglobin of destroyed red cells calculation of the mathematic relation between the excreted pigment and the total mass of hemoglobin should be a more reliable indicator of the degree or rapidity of

(5) A ch Int M d 70 7 87 N v mbe 194

pulp [or possibly that it is more dangerous osmotically speaking for an already fragile erythrocyte than for a normal erythrocyte to be equally delayed in the spleen —Eds]

Dameshek s suggestion that the spherocytes in familial hemolytic anemia are produced in some way by the action of a hemolysin or abnormal metabolite on normal cells appears unlikely in view of the results of these experiments unless the hypothetical hemolytic agent is strictly specific for the patient s own cells

Familial Hemolytic Anemia (Acholuric Jaundice) with Particular Reference to Changes in Fragility Produced by Splenectomy J V Dacie (King s College Hosp London) reports a study of 24 patients The fragility curves before splenectomy although variable in form could be classified into three groups according to shape tailed diagonal and normal type curves (Fig 43) Only 1 of the 24 curves was intermediate in type

Tailed curves were found in 12 cases in these hemolysis could first be detected with saline of concentration between 0 76 and 0 58 per cent and only gradually increased with diminishing saline concentration until a point was reached at which 10 20 per cent of the erythrocytes were broken up Beyond this critical point the curve became abruptly steeper and of approximately the same slope as that of a normal person

Diagonal curves were found in six cases in these hemolysis was first perceptible with saline between 0 80 and 0 68 per cent and increased fairly steadily as the concentration was reduced In four of the cases there were one or more flattened zones toward the middle of the curve

In the five cases with normal type curves the increase in fragility was only slight lysis was first apparent with saline between 0 54 and 0 46 per cent and the curves were of normal shape falling within normal limits of

(7) Quart J Med 12 101 118 Apr 1943

don Blood Supply Depot) found that in five of six patients with familial hemolytic anemia the rate of disappearance of the normal donor cells was normal and the total survival time was 100 130 days In the sixth case destruction was more rapid and was complete in about 60 days

The survival of erythrocytes from a patient with familial hemolytic anemia in a normal recipient was also investigated Blood taken from this patient before splenectomy was completely eliminated by the normal recipient within 14 days of transfusion The survival time may have been less than 14 days but no intermediate observations were made Normal blood given to the same recipient at the same time survived normally Blood taken from the same patient with familial hemolytic anemia a year after splenectomy again rapidly disappeared from the circulation of a normal recipient after transfusion Only 32 per cent of the donor cells were present at the end of 8 days and destruction was complete within 19 days

These observations support the hypothesis that the basic abnormality in familial hemolytic anemia is erythrocyte formation with an increased tendency to hemolysis and cannot be reconciled with any theory which assigns a major role to abnormal destructive mechanisms Ham and Castle have postulated that intravascular stasis is an important factor initiating cell destruction in both the normal and the abnormal spleen and since histologic studies suggest that stagnation does occur to an abnormal extent in familial hemolytic anemia it is at first sight difficult to reconcile these findings with the views of Ham and Castle A possible solution is given by the hypothesis that stagnation is selective while normal discoidal cells have no difficulty in traversing the spleen spherocytes possibly because of their spheroidal shape are trapped within the splenic

(6) Lancet 1 550 552 May 1 1943

of three cases studied more completely on the day of operation, an increase in fragility was produced by anesthetization and a further substantial increase had occurred by the time operation was concluded The histopathology of the spleen was studied in 12 cases Great engorgement with blood was the most notable feature Perfusion experiments with excised spleens failed to demonstrate the cause of congestion Although it was difficult to free the pulp from blood by perfusion with saline the time of circulation of test objects through the spleens appeared normal

Available evidence suggests that this disease is a hemolytic disorder based on the presence of erythrocytes with an increased tendency to hemolysis Although there is much evidence to support the view that this represents a primary defect in erythropoiesis experimental and clinical observations on the relationship between hemolytic anemia splenic congestion and spherocytosis indicate that the possibility of the presence of an abnormal hemolytic agent or metabolite cannot be ignored

Acute Hemolytic Anemia in Fertilizer Workers Robert Wilson Jr and George H Mangun[8] (Charleston S C) report three cases of acute hemolytic anemia with hemoglobinuria occurring in workers unloading fish scrap from ship holds Arsenic is a frequent contaminant in commercial sulfuric acid and the bacterial activity of the scrap would favor reduction reactions productive of arsine The anemia most likely resulted from exposure to arsine gas which accumulated in the hold One case is presented here

Negro 28 complained of headache vomiting and passage of red urine The previous day he had been unloading fish scrap from the ship s hold On examination some pallor was noted and the scleras were thought to be slightly icteric He was quiet in no pain and breathing easily Blood pressure was 170/120 There was generalized enlargement of the lymph nodes the remainder of the examination was negative

Urinalysis disclosed gross hemoglobinuria a large amount of protein but no appreciable number of red blood cells This

(8) S uth M J 36 1 18 M h 1943

the slope which was previously described by Vaughan

Repeated observations were made on nine patients before and after splenectomy Seven had tailed curves they all showed 24 hours after operation a transient increase in median fragility (i e, the concentration of saline giving 50 per cent hemolysis) There was no appreciable alteration in the point of initial lysis at this time, but the shifting to the right of the steep middle part of the curve indicated an increased proportion of the fragile cells previously present in only small num

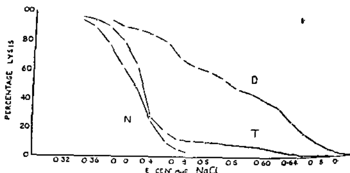


Fig 43 —Quantitative fragility curves from three patients with familial hemolytic anemia D diagonal curve T tailed curve N normal curve

bers and responsible for the tail of the curve By the third day after splenectomy a reduction in fragility was evident and during the latter half of the first weel the median fragility in all the cases fell toward the pre operative level the tails of the curves having by then largely disappeared [It is our belief that these 'tails' are due to a small percentage of cells which have after being rendered more fragile by sojourn in the spleen escaped again into the circulation —Eds] By the tenth day the shape of the curves was nearly normal and median fragility at or slightly below the preoperative level In two cases studied for 13 to 15 months after splenectomy the fragility showed only minor fluctuations and remained well outside normal limits In each

sary for its activity After heating to 56 degrees for two hours its activity was not destroyed but complement (guinea pig serum) and normal blood serum and plasma would then inhibit its hemolytic activity In larger amounts normal blood plasma inhibited the hemolytic effect of the unheated extract but not after the solution of hemolysin has been previously extracted with ether

The authors suggest that after its absorption through the lungs arsine enters into some loose chemical combination with protein in the serum or in the red blood cell itself It may then be supposed that this combination alters the protein so that it acquires an active hemolytic property independent of the presence of arsenic The hemolysin is apparently present in the blood in the early stages of intoxication when it causes widespread blood destruction and it is excreted in the urine Such a hypothesis would explain the finding of a hemolysin in the blood of the first patient shortly after exposure to the gas and the failure to find it in the other patients several days after exposure

One important clinical fact illustrated by observations on this group is the necessity for maintaining an alkaline urine in cases of hemoglobinuria in order to minimize precipitation of hemoglobin in the renal tubules In the one case in which this was inadvertently omitted death occurred

The Clinical Significance of the Rh Factor is discussed by K E Boorman B E Dodd and P L Mollison[9] (S W London Blood Supply Depot) The discovery of this factor has disclosed the reason for many hemolytic reactions following certain homologous group blood transfusions and has also facilitated understanding of the hemolytic anemias of the new born Human erythrocytes contain in addition to the A and B agglutinogens of Landsteiner a variety of antigenic components These other antigens of which M and N have hitherto been the best known are usually ignored in

(9) B t M J 53 38 N 695 N v 14 194

condition persisted for almost six days after which it began to clear Three days later he was discharged with a normal urine Slight transitory icterus developed and there was moderate subjective weakness due to anemia, but these disappeared after the blood loss had topped Treatment was purely symptomatic transfusion was planned but a suitable donor was not available and iron was prescribed for the anemia

The initial blood count showed 11 Gm hemoglobin, 3 930 000 *erythrocytes and 12 200 leukocytes four days later* the hemoglobin had fallen to 5 5 Gm and the red count to 1 920 000 Blood smears were negative for plasmodia and for sickling The Donath Landsteiner test performed after the blood serum had cleared, was negative The fragility test showed no increase in the fragility of the erythrocytes to hypotonic saline

Other investigators have demonstrated the in vitro effect of hemolysins in the blood serum of patients with acute hemolytic anemia by direct observation of the hemolytic effect of the serum on the erythrocytes In these cases however the presence of hemoglobin in the serum made direct hemolytic tests impossible To circumvent this obstacle a technic was devised whereby the hemoglobin was largely separated out and solutions containing various fractions of the blood serum were prepared This technic in Case 1 showed the active hemolytic agent to be contained in the protein (globulin) fraction of the blood serum It was not dialyzable its activity was inhibited by the presence of ammonium sulfate and it was present in high concentration Complement was unnecessary for its action and its activity was destroyed by heating to 56 degrees for two hours

It was not possible to demonstrate this hemolytic activity in the serum of the other two patients From the urine in *Case 3* however there was obtained a *solution* of protein (pH 7 25) which had a remarkably active hemolytic effect against all types of washed red blood cells By the time this solution was prepared the patient had died and no tests could be made against the patient s own cells The hemolysin was contained in the protein of the urine and was not dialyzable It was present in high concentration and complement unneces

anti A or anti B agglutinins were observed This observation supports the idea that anti A or anti B agglutinins may occasionally cause destruction of fetal erythrocytes of group A or B and thus be the chief etiologic factor in some cases of erythroblastosis foetalis

In 8 cases it was not possible to demonstrate Rh agglutinins in the infant s serum from 3 to 10 days after birth This is not surprising however since these antibodies are not usually present in high titer in the mother s serum and since they will be expected to be absorbed on to the infant s (Rh positive) cells for the first time They were however demonstrated in the serums of identical twins within 24 hours after birth

In the present series Rh antibodies were found far more frequently than in the series described by Levine and co workers This is ascribed to refinement in technic Levine s technic consisted in incubation of the mixture of cells and serum (30 60 minutes at 37 C) followed by centrifugation at low speed (500 r p m) for one minute and by gentle shaking to resuspend the sediment The tubes were then examined macroscopically for evidence of agglutination and apparent negatives were examined microscopically The authors have found that this technic is not so sensitive as that of simply allowing the mixtures to stand in the incubator for two hours followed by examination of the pattern of the sediment and withdrawal of a portion of the sediment for microscopic examination Even the gentle shaking of the tubes advised by Levine *et al* may completely abolish a weak reaction It is of course necessary to carry out control tests with Rh negative cells if weak reactions are to be accepted as evidence of the presence of an Rh antibody

The authors also record finding weak Rh antibodies in the serums of the mothers of some babies with physiologic jaundice This suggests that there is no clearcut distinction from the clinical point of view between mild and severe jaundice of the new born

At present if serologic tests are used as an aid in the

selection of blood donors because the corresponding anti bodies occur but rarely in human serums and, moreover, these factors rarely stimulate production of immune anti bodies in man By contrast, the importance of the Rh factor lies in its ability to stimulate formation of specific immune agglutinins in man

The presence of the Rh factor in certain human *erythrocytes* was first discovered by *testing samples with* anti rhesus serums prepared by injecting the blood of rhesus monkeys into rabbits It was found that 85 per cent of human bloods, irrespective of group were agglutinated whereas 15 per cent were not The former are termed Rh positive and the latter Rh negative Persons with Rh negative erythrocytes are capable, under certain circumstances of forming an antibody which reacts with the Rh antigen This may occur after transfusions of Rh positive blood or probably more commonly when a woman (herself Ph negative) becomes pregnant with a baby whose erythrocytes are Rh positive

In regard to the heredity of the Rh factor Landsteiner and Wiener suggested that two allelomorphic genes—Rh and rh—were concerned Rh being dominant When the husband s phenotype is Rh positive and that of the wife Rh negative the phenotype of the baby will depend on whether the husband s genotype is RhRh or Rhrh If it is the former the infant s genotype will always be Rhrh and the phenotype therefore Rh positive if it is the latter the phenotype will be Rh positive in only 50 per cent of the siblings That tests for Rh antigens and anti bodies have considerable application in clinical medicine is confirmed by others and also by some new findings of the authors

In a series of 48 cases of definite erythroblastosis foetalis an immune agglutinin incompatible with the infant's erythrocytes was found in the mother s serum in every case In 44 this agglutinin was anti Rh, although in some of them immune anti A or anti B agglutinins were also found In the remaining four only immune

Levine and Helena Wong[1] (Newark Beth Israel Hosp) that a correspondingly low incidence of Rh negative individuals would be found in a random Chinese population This was confirmed in a study of 150 Chinese persons only 1 of whom was Rh negative The contrasting distribution of Rh positive and Rh negative reactions among white and Chinese individuals as tested with three varieties of human anti Rh serums is given in the table

AGGLUTINATION REACTIONS WITH HUMAN ANTI RH SERUM

No Tested	Anti Rh		Anti Rh		Anti Rh	
	+	—	+	—	+	—
334 white	87 0	13 0	85 0	15 0	73 0	7 0
150 Chinese	99 3	0 7	99 3	0 7	9 0	0

In agreement with Landsteiner and Wiener the terminology used in the table is employed for the differentiation of the three varieties of human anti Rh serums It is based on Levine s observation that the anti Rh serum$_1$ contains more than one antibody

As indicated elsewhere anti Rh$_1$ or anti Rh$_1$ serum is of far greater significance for diagnosis of erythroblastosis foetalis than anti Rh serum With anti Rh$_1$ serum which may be considered standard Rh negative individuals are 21 times less frequent among Chinese than among white groups Accordingly this observation serves as a basis to support the contention that erythroblastosis foetalis is rare among Chinese infants A search of the literature revealed only one genuine case in a Chinese infant reported in 1932 by Ku and Li The files of the *Chinese Medical Journal* from 1916 to date fail to reveal the report of any other proved cases

Erythroblastosis Foetalis (Acute Hemolytic Anemia of the New Born) The concept that erythroblastosis foetalis is primarily an acute hemolytic anemia of the new born due probably to an agglutinative hemolytic process is not new Support has recently been ac

(1) Am J Obst & Gyn 45 83 84 M 1943

diagnosis of doubtful cases of erythroblastosis compatibility of the mother's serum with the infant's erythrocytes may be regarded as a strong point against the diagnosis, provided the mother s serum is examined by a sensitive technic 7 21 days after delivery On the other hand, if the mother s erythrocytes are shown to be Rh negative and her serum is found to contain anti Rh agglutinins the diagnosis is strongly supported

A change in the method of selection of blood donors in certain cases is urgently needed This applies particularly in the case of transfusion of recently delivered women and above all whenever there is any suspicion that the infant is affected with erythroblastosis or when there is any previous history of the birth of jaundiced babies or of stillbirths without obvious cause At the same time modification of the present method of testing for compatibility between the bloods of donor and recipient must be made Methods for carrying out these tests are described and compromise procedures are discussed for cases in which there are no facilities for making these tests

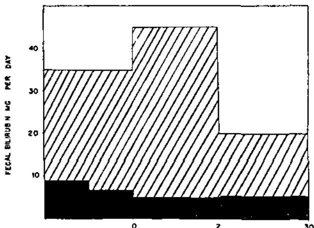
It is recommended that every blood bank take steps to establish a panel of group O Rh negative donors whose blood will be available first for the transfusions referred to here and secondly for use as a routine in the transfusion of infants affected with erythroblastosis (when necessary)

Incidence of the Rh Factor and Erythroblastosis Foetalis in Chinese There is already evidence that the incidence of the Ph factor is different in the white and in the colored races Thus with a particular human anti Rh serum there are 15 per cent Rh negative white individuals in contrast to 5 to 8 per cent Rh negative colored individuals This is paralleled by the greater incidence of erythroblastosis foetalis among white than among colored infants The rarity of erythroblastosis foetalis among Chinese infants suggested to Philip

ranged from 0 5 to 29 7 with an average value of 9 6

In the three cases of erythroblastosis foetalis the fecal bilirubin excretion ranged from 19 4 to 109 mg per day during the first 15 days of life The hemolytic index was extremely high ranging from 71 to 293 in the same period

Values for the fecal excretion of urobilinogen by the normal infants ranged from a trace to 0 70 mg per day



F g 44 —C mp son of f c l tput f b l rub n f rm l (black) nd eryth bl t t (b rr d) f t Bil b ntp t f yth obl t ti i f nt t em ly h gh omp d w th th t rm l nfa ts D y f l fe e pl tt d b s

while the erythroblastotic infants excreted 0 25 11 mg per day Although the exact nature of the hemolytic mechanism in erythroblastosis foetalis may be disputed results of this study indicate strongly that the condition is fundamentally one of increased breakdown of blood

Skeletal Changes Associated with Erythroblastosis Foetalis Richard H Follis Jr Deborah Jackson and William H Carnes[3] (Johns Hopkins Univ) report five cases of erythroblastosis foetalis and emphasize changes

(3) J P d t 1 809 J l 1942

corded this concept by studies of the Rh factor Also there is much indirect evidence pointing to the hemolytic nature of erythroblastosis foetalis i e, anemia jaundice and indirect bilirubinemia, together with indications of increased myeloid regenerative activity in the peripheral blood such as presence of nucleated red cells, reticulocytes and myelocytes The extreme *erythroblastic hyperplasia of the bone marrow* and the marked extramedullary hemopoiesis in the spleen and liver are also indicative of the reaction to a hemolytic process However direct *proof* of the hemolytic nature of the disease must lie in the quantitative demonstration of increased excretion of derivatives of the breakdown of hemoglobin i e bilirubin and its products William Dameshek, Tibor J Greenwalt and Russell J Tat[*] studied the fecal output of urobilinogen and bilirubin of three infants with erythroblastosis foetalis and compared the results with those for a series of normal new born infants

Determinations of fecal bilirubin were performed by Malloy and Evelyn s method Fecal urobilinogen was estimated by Watson s method The hemolytic index was calculated from the formula

$$\frac{\text{Total bilirubin} + \text{total urobilinogen per day in mg} \times 100}{\text{Total circulating hemoglobin in Gm}}$$

The hemolytic index expresses the number of milligrams of bile pigment derived from each 100 Gm circulating hemoglobin and is therefore a far better indicator of the degree of hemolysis than is the figure for the total daily excretion of the hemoglobin derivatives alone

For the eight normal infants bilirubin values during the first five days of life were 1 23 mg per day, with an average excretion of 8 6 mg in the next five day period values were 0 16 mg per day, with an average excretion of 5 7 mg and from the tenth to the fifteenth day the range was 0 3 to 12 4 mg per day with an average excretion of 5 3 mg The hemolytic indexes of these infants

(*) Am J Dis Child 65 571 581 Ap Il 1943

change and there was nothing to indicate the presence of new bone formation within the periosteum

The exact mechanism for the increase in density is



Fg 46—S m p d g D ff m u t f b t t l ge h ft j n t n and f rthe d w wh d d ty f u d

obscure These changes could be due to the influence of some substance elaborated by the maternal organism or placenta The placenta in erythroblastosis foetalis is frequently enlarged and has been reported to contain excessive chorionic hormone Estrogenic hormone has been shown to increase the density of bones of birds and

in the skeletal system heretofore undescribed The most striking skeletal alteration was marked increase in density of the bones (Figs 45 and 46) consisting of an increase in number and thickness of trabeculae due apparently to lack of destruction of the calcified car



Fi 45 —F lms f f m t b a and fibula show as of d cr a ed d n ty t end of b n and n d d n ty c te of shafts

tilaginous matrix substance which was covered with a thick layer of bone In two cases this increase was uniform throughout the entire shaft while the other three showed zones of decreased density of varying width a short distance below beneath the lattice at the cartilage shaft junction One had a band of increased density beneath the zone of rarefaction The cartilage showed no

present The accompanying anemia is usually ascribed to reduced marrow space but the possibility that some more fundamental disturbance affects both hemopoiesis and bone formation has also been advanced

Sickle Cell Anemia in the White Race Maurice Morrison A A Samwick and Eva Landsberg[4] (Jewish Hosp Brooklyn) point out the value of splenic puncture and study of splenic tissue for evidence of sickling when it is not apparent in the peripheral blood and record instances of sickling in two additional white families [There is no need for splenic puncture as the peripheral blood when deprived of oxygen will always do as well for microscopic inspection —Eds] The ancestors of both families were born and lived in Italy one family originating in Catania and the other in Calabria The parents of the patients emigrated to the United States The sickling phenomenon was clearly demonstrated in members of both families the trait having been transmitted for three generations

One patient presented various gradations of sickle cell anemia from that of sickle cell trait in one admission to a sickle cell crisis in the last admission Because the patient was white many opportunities for making the diagnosis were missed Complicating episodes in the progress of the trait were associated with anoxemia (pneumonia alveolar abscess pyuria with administration of mandelic acid etc)

The second case illustrated the difficulty of differentiating primary hemolytic disorders from hemolytic episodes following sulfonamide therapy The drug was readily ruled out since there was a recurrence of the hemolytic picture after 10 months during which time no sulfonamides were given Hemolytic icterus was ruled out because of persistent normal results of fragility tests Satisfactory explanation for the hemolytic disorder was still lacking since the complicating incompatibility with regard to the Rh factor had been forgotten A splenic

(4) Am J Dis Ch ld 64 881 887 No mbe 194

young animals but no observations have been made on animals whose mothers received large amounts of estrogen during pregnancy

Another factor meriting consideration is that some material liberated in the breakdown of red cells plays a role Although analyses of the bone have not been made analogy is drawn between the possible role of excessive iron liberated by such cellular breakdown and the changes following lead poisoning in childhood which include an increase in the amount of cartilaginous matrix substance beneath the cartilage shaft junction Bismuth likewise produces a zone of increased density in the growing bones of infants whose mothers have had injections of this element during pregnancy

Skeletal changes associated with the chronic hemolytic anemias of childhood are also considered In these cases however there is rarefaction of the long bones Similar changes are seen in leukemia The thickening of the skull described in cases of chronic hemolytic anemia is more difficult to explain but apparently is due to hyperplasia of the marrow and pushing up of the periosteum covering the outer table These cases therefore differ from those under consideration However, in utero blood formation takes place in the extramedullary tissues with great ease and hyperplastic marrow does not affect the bone as it does in postuterine life

Changes in skeletal roentgenograms similar to those described in three cases are frequently encountered in congenital syphilis However serologic tests were negative and no focal inflammatory lesions were seen in the microscopic sections or localized areas of destruction in the roentgenograms

The disease par excellence in which there is a persistence of calcified cartilaginous matrix substance on which bone deposits is osteosclerosis fragilis generalisata (Albers Schonberg s disease) Deep in the shaft large amounts of blue staining calcified matrix substance are found encased in bone or in osteoid when rickets is

patients when they were having abdominal or muscular pain did not regularly give relief However soon after the flow of oxygen was started the percentage of sickle cells in both venous and arterial blood decreased definitely often from over 40 per cent to less than 20 per cent in the venous circulation This change persisted as long as pure oxygen was breathed The oxygen content of the arterial blood increased so that it equaled or exceeded the oxygen capacity No consistent change occurred in urobilin excretion however to indicate that the rate of hemolysis had been materially altered The most dramatic results of prolonged oxygen administration were (1) a fall in reticulocytes which usually began the fourth to sixth day and lowered the level from the initial 20 30 per cent to as low as 1 per cent and (2) a fall in the erythrocyte count which usually began the sixth to eighth day and was as great as 500 000 1 500 000 cells After oxygen was discontinued the reticulocytes began to increase and reached a peak of occasionally more than 50 per cent on the fifth to eighth day A shower of normoblasts appeared with the reticulocytosis At the same time a rise in red cell levels began and continued until the pre oxygen level was attained These results are interpreted as indicating that administration of nearly 100 per cent oxygen depresses erythropoiesis an effect which might be the physiologic antithesis of the erythroid stimulation produced by low oxygen tensions It is suggested that this result has not been noted in previous studies when high concentrations of oxygen were given normal persons and individuals with polycythemia because the length of red cell life is so great that the decreased rate of erythrocytogenesis would not be evident for long periods Patients with sickle cell anemia show the effect more quickly because the reticulocyte level is elevated and the rate of red cell destruction accelerated

No distinct toxic manifestations of the oxygen administration were noted except for inflammation and con

puncture revealed erythroblastosis with marked sickling

Bone marrow aspirations in both patients showed great increase in erythrogenesis associated with a maturative defect of the erythrocytes *Cell destruction* (poikilocytosis microcytosis polychromatophilia, etc) was evident in the peripheral smear These cases demonstrate that search for the sickling phenomenon should be undertaken in all cases of obscure hemolytic disorders *even in* white patients and if possible a splenic puncture should be done when splenomegaly is present

[Moral think of sickle cell anemia as the cause of "obscure" hemolytic anemia in white persons of Mediterranean origin then do a sickling test on the peripheral blood and you will know We too have forgotten this in the past —Ed's]

Effect of Breathing 80 100 Per Cent Oxygen on Erythrocyte Equilibrium in Patients with Sickle Cell Anemia Edward H Reinhard Carl V Moore R Dubach and Leo J Wade (St Louis) attempted to determine whether oxygen tension of arterial blood could be raised sufficiently to decrease the intravascular sickling of red cells It was thought that this might accomplish (1) a reduction in rate of hemolysis with consequent lessening of the degree of anemia and (2) relief of pain during sickle cell crises Three patients were observed six different times After control periods of 4 to 8 days the subjects were fitted with a Boothby Lovelace Bulbulian mask and given pure oxygen without intermission for 8 to 20 days Red cell counts hemoglobin levels and reticulocytes were estimated daily Determinations of serum iron and of oxygen content and capacity of both arterial and venous blood were made every four days Excretion of urobilin in urine and feces was measured by Watson's method as an index of the rate of hemoglobin destruction The percentage of sickle cells in arterial and venous blood was determined regularly by Sherman's method Alveolar oxygen content was measured on several occasions

Administration of nearly 100 per cent oxygen to these

(5) J A M A 1 1 124 1 46 Ap l 10 1943

culi in all cases The cholelithiasis was not the cause of any episodes of colicky pain obstructive jaundice or clay colored stools before splenectomy

Neither the usual conservative treatment nor splenectomy modified the course of the disease In one case the spleen weighed 552 Gm Pigmentation was marked some of it was in the phagocytes and some free in the intercellular spaces The sinusoids contained many large phagocytes Reticulum cells were proliferating Many mature polymorphonuclear neutrophils were scattered throughout the tissue There was a moderate number of eosinophils Numerous nucleated red cells were present frequently arranged in clusters showing various stages of maturity Examination of bone marrow showed that before surgery 78 per cent of the nucleated forms were normoblasts and after surgery 43 per cent with a corresponding rise in the more mature forms of neutrophils

[Assuming that all fi e cases were of the same type and that one patient had symptoms for over five years the vari t es of hemolytic anemia wh ch would not be diagnosed by the authors usual diagnost m thods for blood spleen or marrow would be (1) paroxysmal noctu nal hemoglobinuria and ( ) sickle cell anemia The fi st is favored by the constant presence of leukop nia noted here The plasma and urine were apparently not stud ed for the p esence of free hemoglob n Th proof would be the demonstration of hemolys s on bubblin pure carbon diox de through the *defibrinated* blood (T H Ham) This will also cause sickl ng to appear f that trait s p esent Here it seems unl kely but it does occu rarely in white persons espec ally of Med terranean origin (see th s YEAR BOOK p 51) Splenect my does not ben fit these cond t on —Eds]

gestion of the upper respiratory mucosa After oxygen was discontinued two patients became nauseated and had headache for 24 to 48 hours

Refractory Hemolytic Anemia John C Sharpe and J Perry Tollman[6] (Omaha) present hematologic and pathologic observations on five adults with refractory hemolytic anemia treated with splenectomy Onset was usually insidious Symptoms varied from three months to five years in duration with alternating periods of remission and relapse They included pallor, weakness hemolytic type of icterus gastro intestinal disturbances dizziness and dyspnea on exertion Constant features were weight loss and low grade fever All patients had splenomegaly The liver was slightly enlarged in two During episodes of acute blood destruction there was acute exacerbation of all signs and symptoms with increased jaundice pallor fever and splenomegaly Epigastric distress sometimes became colicky Hemoglobin content and red cell count decreased rapidly within 24 to 48 hours No direct cause could be elicited for initiation of these attacks In two cases the crisis immediately followed transfusion of whole blood Anemia was severe with the erythrocyte level just at or under 1 000 000 cells per cu mm in three cases Erythrocytes were of the macrocytic type in three cases the mean corpuscular volume averaging 118 cu μ for the whole group and the mean corpuscular hemoglobin concentration 31 per cent Reticulocytosis was a striking feature in three cases the reticulocytes averaging 39 2 per cent for the group No spherocytes were found in stained blood smears in any case Fragility tests carried out before and after splenectomy showed no significant abnormality Bleeding and clotting times and platelet counts showed little change in three cases and were somewhat decreased in two Preoperative investigation showed definite and persistent leukopenia the white cell count ranging from 1 400 to 4 000 per cu mm Cholecystograms revealed biliary cal

(6) Arch Int Med 70 113 July 1942

tissues by presence of hematin in the plasma and by increased porphyrin and urobilin excretion Studies of 24 hour excretion of urobilin in the urine of 10 patients with pernicious anemia revealed values ranging from 400 to 1 200 mg (normal 100 to 200 mg) All manifestations of increased hemolysis disappear however in 48 hours after beginning of liver therapy

The disturbed iron metabolism in pernicious anemia is noteworthy Aside from the increased hemosiderin content of the organs notably liver and spleen the serum iron level as in other hemolytic anemias rises to almost double the normal value With the beginning of liver therapy the serum iron content falls and is lowest when hemolysis has ceased and iron utilization by the bone marrow is greatest i e at the peak of the reticulocyte response The hemoglobin ratio rises and with its normalization the serum iron content likewise reaches normal values In about half the cases however the hemoglobin rises only to 60 to 70 per cent (Sahli) and since the number of erythrocytes continues to increase hypochromic anemia may supervene Consequently the serum iron content becomes further reduced In such cases it must be assumed that either the iron reserves have been depleted or not enough iron is freed for formation of hemoglobin Institution of iron therapy restores both hemoglobin and serum iron content to normal

Pernicious Anemia Due to Deficiency of Extrinsic Factor Stuart P Townsend and F B Begor[8] (Montreal) present a case of anemia believed to be due to deficiency in protein causing deprivation of the extrinsic factor

Man 56 with tentative diagnosis of pernicious anemia or gastric carcinoma had not felt well for years tired easily and had cardiac pains on exertion or excitement He frequently had indigestion characterized by epigastric pain abdominal cramps anorexia and nausea For four months he had had alternating periods of diarrhea and constipation and became progressively weaker For 20 years he had been a vegetarian

Physical examination showed undernourishment a lemon

(8) C n d. M A J 47 35 354 O t ber 1942

PERNICIOUS ANEMIA AND RELATED MACROCYTIC ANEMIAS

In this section articles on the treatment of the pernicious anemia of pregnancy are of especial interest —Eds

The Sphere of Action of the Hemopoietic Principle goes far beyond formation of erythrocytes in the opinion of C D de Langen[7] (Univ of Utrecht) The author has previously pointed out that Castle's theory does not explain satisfactorily many clinical observations in pernicious anemia especially the important factor of increased hemolysis If impaired erythropoiesis were the sole factor in pernicious anemia the degree of anemia would determine the intensity of all other symptoms which is definitely not the case From a standpoint of treatment this seems still more convincing Thus, soon after beginning liver therapy the patient s general condition improves strikingly in contrast to the much slower progression of erythropoiesis which does not set in until the fourth or fifth day i e at the time of reticulocyte crisis Oral symptoms fever increased basal metabolic rate and increased urobilin excretion subside within the first few days of specific treatment when the anemia has not yet changed Assuming lack of building material for formation of erythrocytes to be the only factor responsible for pernicious anemia does not explain the occurrence of trophic disturbances glossitis cord symptoms polyneuritis or psychic manifestations

[Glossitis and neural lesions have been discussed by Castle and many others as manifestations of the conditioned deficiency in pernicious anemia C P Rhoads has demonstrated experimentally how defective nutrition may permit increased blood destruction in the presence of toxic substances —Eds]

Few investigators will deny that increased hemolysis is an important feature of pernicious anemia This is attested by the pale straw colored tinge of the skin caused by increased urobilin content of plasma and the

(7) G st oe te ol gi 66 86 97 194

severe prolonged vomiting and 8 edema of the legs Edema was related to low hemoglobin levels rather than to decreased serum protein levels Thirteen had sore tongue usually an early and often a transient or recurrent symptom Fever of 100 to 101 F was usual and often confused diagnosis under treatment it usually regressed in about 10 days Ten patients had retinal hemorrhages Two had actual glossitis 3 a palpable spleen and four enlarged liver Three had histamine refractory achlorhydria and 7 had hypochlorhydria

Hemoglobin content ranged from 10 to 60 per cent (Sahli) being between 10 and 20 per cent in 11 patients Red blood cell count in 18 patients ranged from 500 000 to 1 500 000 Color index ranged from 0 98 to 1 4 average 1 13 average reticulocyte value was 3 per cent Mean corpuscular volume varied from 96 7 to 157 cubic microns average 110 Blood films showed marked anisocytosis with poikilocytosis microcytosis and megalocytosis and diffuse polychromasia spherocytosis was suggested but not proved Three of nine patients showed insignificant increase in red cell fragility Six showed excessive urine urobilinogen van den Bergh s reaction in all cases was positive indirect and average bilirubin was 1 9 units White blood cell counts ranged from 12 200 to 1 300 per cu mm average 5 200 As a leukocyte count of 15 000 is common after normal delivery there appeared to be definite leukopenia Differential counts in 10 cases showed normal relationship of myeloid and lymphoid cells

With normal free hydrochloric acid in the gastric juice and history of poor diet response may be obtained with ½ oz marmite [autolyzed yeast—Eds] daily in a good mixed diet However marmite is often poorly tolerated With achlorhydria or when marmite fails purified liver extract such as anahemin may be given intramuscularly every four days in 5 cc doses If this fails comparable doses of crude liver extract such as campolon may be tried or ½ lb raw or lightly cooked liver

yellow cutaneous tint, increased bile pigments in blood and a smooth tongue Free hydrochloric acid was present in normal quantities Hematologic findings were erythrocytes, 1,930,000 erythrocyte diameter, 8 4 μ (modal), hemoglobin, 48 per cent platelets 194,000 leukocytes, 5 400, with polymorphonuclears 43 per cent lymphocytes 53 per cent, basophils 1 per cent eosinophils 3 per cent Most erythrocytes were macrocytes with 4 per cent reticulocytosis

Analysis of his diet showed marked protein deprivation The only biologic (grade A) protein was obtained from small amounts of milk and cheese On these findings, anemia was considered due to protein deficiency and he was placed on a high protein diet, exclusive of liver No other medication was given Shortly after introduction of meat in the diet there were marked reticulocyte response, rapid increase in erythrocytes and hemoglobin and decrease in cell size He had pronounced gain in weight and feeling of well being

Adequacy of increased protein in diet is stressed Treatment with liver may obscure diagnosis and confine the patient to a life regimen that is unnecessary and expensive Many similar cases may be encountered during the war especially in countries with serious food shortages

[It should not be inferred that the active therapeutic agent here was necessarily protein it may like extrinsic factor be closely associated with but not identical with protein. This does not alter the practical fact that protein is desirable in the diet —Eds]

Pernicious Anemia of Pregnancy H G Miller and T C Studdert[9] (Newcastle on Tyne) report on 23 patients aged 22 41 Average parity was four Of 19 with history of adequate diet 7 had gross deficiency of proteins and vitamins although none of the 23 had polyneuritis or signs of vitamin deficiency In 12 with adequate diet vomiting was severe and prolonged and in some edema and vomiting were aggravated by a protein free diet for supposed toxemia Serum protein in five cases ranged from 5 12 to 6 3 per cent serum calcium in six ranged from 9 5 to 10 5 mg per 100 cc Individual readings bore no apparent relation to dietary history

Symptoms on the average appeared at the seventh month All had pallor 22 breathlessness and fatigue 11

(9) Lancet 33 334 Sept 19 194

cause For this reason the term megaloblastic anemia of pregnancy is proposed as a substitute for pernicious anemia of pregnancy " on the grounds that the megaloblastic appearance of bone marrow is characteristic and constant while peripheral blood findings vary Sternal marrow studies are necessary for adequate diagnosis and desirable for establishment of rational therapy

All patients were given liver extract parenterally In five this resulted in typical reticulocyte response within a week and subsequent adequate rise in erythrocyte count Ten were temporarily refractory to treatment for from 11 days to several months All refractory patients received iron in addition to liver extract and many also received yeast and ascorbic acid In 12 blood transfusion was necessary until response to liver therapy was obtained

Etiology is unknown Temporary failure of secretion of Castle s intrinsic factor impairment of secretion of hydrochloric acid reduced intake of extrinsic factor impaired absorption from the small intestine and increased demands for hematinic principles are possible factors

Recognition of anemia during pregnancy is of paramount importance as only by this means can acute exacerbations during the last two months be prevented Good prognosis is possible even in refractory cases if life is maintained by transfusion while persevering with vigorous hematinic treatment

Macrocytic Anemia of Pregnancy and Puerperium H W Fullerton (Univ of Aberdeen) describes three ca es in which little or no improvement in blood level followed parenteral liver extract therapy but in which rapid regeneration occurred when this treatment was supplemented by ingestion of whole liver In each case the degree of anemia was so severe that separate trial of different therapeutic agents was not justified Accordingly massive treatment with parenteral liver extracts

( ) B t M J 1 158 160 F b 6 1943

daily causes dramatic response Response to the raw liver is not attributed to the iron content but to a hemopoietic factor lost in the process of preparing liver extract Transfusions are given only if the hemoglobin level is desperately low All the authors' patients responded to specific therapy

Megaloblastic Anemia of Pregnancy and the Puerperium L S P Davidson, L J Davis and James Innes[1] (Univ of Edinburgh) describe a severe type of anemia of pregnancy associated with megaloblastic bone marrow and differentiate it from Addison's pernicious anemia They report findings on 16 cases Age was considerably lower than in Addison s anemia 50 per cent of the patients were primiparas although pernicious anemia occurs mainly in multigravidas Only 2 were seen before delivery but records revealed pallor and dyspnea in 13 and low hemoglobin in 8 Anemia became progressively more severe during the last two months of pregnancy

The authors believe a blood picture displaying anisocytosis macrocytosis ovalocytosis hyperchromia leukopenia and thrombopenia and histamine fast achlorhydria should be present to justify diagnosis of addisonian pernicious anemia In none of the 16 were all these present Red cell counts varied from 570 000 to 3 200 000 but were below 1 700 000 in 11 Hemoglobin concentration ranged from 12 to 52 per cent being below 40 per cent in 12 Ten had color index above unity Anisocytosis and ovality of outline were not as prominent as in classic addisonian anemia Numerous macrocytes were found in nine Leukocyte count was normal in nine leukocytosis was present in four Sternal puncture performed in 13 showed numerous primitive megaloblasts in 12 Free hydrochloric acid was found in 10 of 14 tested Puerperal septic complications developed in nine cases mastitis 4 pyelitis 3 and pneumonia 2

Examination of sternal marrow showed clearly that arrested maturation of megaloblasts was the immediate

(1) Brit M J 2 31 34 July 11 1942

Daily intramuscular administration of 0 25 U S P units of purified liver extract produced a rise in reticulocytes to 26 8 per cent and pronounced clinical improvement After three months administration of liver extract the child weighed 12 lb 8 oz erythrocyte count was 4 480 000 and hemoglobin content 63 per cent Improvement continued during six more months of therapy

Macrocytic hyperchromic anemia other than pernicious anemia can develop in absence of the extrinsic factor of Castle Apparently in the authors case the deficiency was specific for the hepatic antipernicious factor as the small amounts of highly purified extract did not supply any of the known components of vitamin B complex Previous investigators have used powdered liver extract orally and since such extract contains vitamins it has been impossible to determine whether the therapeutic effect was due to the antipernicious principle or the vitamins

Treatment of Pernicious Anemia with an Experimental Proteolyzed Liver Preparation Recent reports have indicated the superiority of whole liver in certain types of macrocytic anemia such as those occurring in pregnancy sprue and tropical nutritional deficiency states occasional cases of these anemias are refractory to purified liver extracts administered parenterally but amenable to whole liver given orally Accordingly it was thought that it might be advantageous to administer to such patients whole liver in a soluble predigested form A predigested product would be assimilated more readily by patients whose digestive and absorptive processes were impaired and could also be given to those allergic to liver extracts injected parenterally

L J Davis L S P Davidson (Univ of Edinburgh) D Riding and G E Shaw[4] (Evans Biological Inst) describe a method for production of a palatable and readily assimilable whole liver preparation proteolyzed liver by means of enzyme digestion of raw liver with papain The product thus obtained is a powder which is completely soluble in hot or cold water In proteolyzed

(4) B M J 1 655 656 May 9 1943

campoferron (oral liver extract with iron Bayer) and whole liver was instituted after the effect of parenteral liver extract had been found to be slight or absent This makes interpretation of results more difficult than if the different forms of therapy had been used separately but analysis of results appears to justify certain conclusions Potency of these liver extracts was proved in other cases Moreover there was no evidence of sepsis or other condition which might have had an inhibitory effect and the rapid blood regeneration which followed massive therapy indicated absence of marrow hypoplasia It is concluded therefore that a deficiency of factors other than the antipernicious anemia principle was concerned in production of the anemia The evidence suggests that ingestion of whole liver provided these factors

Nutritional Anemia in Infant Responding to Purified Liver Extract Paul J Fouts and Elizabeth Garber[3] (Indianapolis) state that macrocytic hyperchromic anemia is usually observed in previously healthy infants after infection of the upper respiratory tract followed by vomiting diarrhea or both Malnutrition is evident and no weight gain follows formula change or vitamin administration Free hydrochloric acid is usually present but frequently decreased Crude liver extract, orally or injected has been followed by reticulocytosis rapid erythrocyte rise and weight gain Anemia does not recur after relief A case is presented

Girl, 4 months weighing 7 lb 6 oz, had begun vomiting after respiratory infection She had weighed 6¾ lb at birth and 8½ lb at 2 months Mother had eaten no meat at gestation Erythrocyte count was 910 000 Whole blood iron ammonium citrates brewers yeast and various preparations of vitamin B complex were administered and discontinued Frequent formula changes produced no weight increase About two weeks later erythrocyte count was 1 790 000 hemoglobin content 36 per cent leukocyte count 5 700 percentage of reticulocytes 1 8 hematocrit reading 16 5 cc volume index 1 0, color index 1 0 and mean corpuscular volume 92 cu μ Gastric analysis 3½ weeks later after histamine stimulation showed normal free hydrochloric acid

(3) Am J Dis Child 64 70 3 August 194

desiccated liver has not been demonstrated here or elsewhere It is over 15 years since the immense convenience of deproteiniz ing liver to concentrate its hemopoietic activity was first clearly established —Eds]

Dosage of Liver Extract in Treatment of Cord Le sions Associated with Pernicious Anemia R Gottlieb (Jewish Gen l Hosp Montreal) reports six cases of per nicious anemia with subacute combined degeneration of the spinal cord to demonstrate the necessity for larger doses of liver extract in such cases In three cases there was rapid improvement of the anemia with small doses of concentrated liver extract but no improvement of the neurologic signs and symptoms until dosage was markedly increased In the other three cases treatment was started with much larger doses and the neurologic signs and symptoms improved much sooner However no better results were obtained with the larger dose so far as the anemia was concerned It is of course recog nized that recovery or improvement will depend on the degree of permanent damage done to the nervous system

Intolerance to Liver Extract in Pernicious Anemia Elizabeth Delikat[6] reports three cases of pernicious anemia in which the patients had become sensitive to parenteral injection of liver extract By use of divided doses of the extract over several weeks it proved pos sible to desensitize two of the patients so that they were able to tolerate their full requirement of liver extract in one injection at monthly intervals In the third case the required dose is being given in small injections over two days without attempt at permanent desensitization Two of these cases are presented here

Case 1 —Man 52 had been under treatment for pernicious anemia since May 1939 receiving a maintenance dose of 4 cc liver extract parenterally every six weeks In October 1940 after the usual injection he developed generalized urticaria with puffiness of the face and failure of vision Thereafter he was treated with liver extract orally until December, 1941 when desensitization was attempted Intradermal skin tests with 0 1 cc of two different brands of liver extract were

(5) C d M A J 48 4 0 4 1 M y 1943
(6) B t M J 1 539 540 M y 1 1943

liver there is present predigested protein material in addition to essential hemopoietic factors Fats fat soluble vitamins and coarse indigestible material are discarded It is estimated that 1 oz proteolyzed liver powder is derived from approximately 6 oz raw "wet" liver, after allowing for losses due to the mechanical process

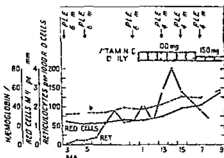
Results of treatment of five typical cases of pernicious anemia with proteolyzed liver are recorded The powder was dissolved in warm water and seasoned with salt and pepper Doses varied from 2 to 8 teaspoonfuls of powder daily equivalent by weight to 2 drachms and 1 oz respectively Without exception a satisfactory response was noted in a few days In one case reticulocyte counts were not available but the progressive improvement in the blood picture left no doubt as to the effect of treatment The other four patients displayed a significant reticulocyte response followed by a progressive amelioration of their clinical and hematologic conditions The average rise in red cells was 940 000 per cu mm during the first two weeks and 1 740 000 during the first three weeks of treatment An adequate daily dose appears to be 2 drachms but in certain resistant cases larger amounts may be desirable This amount is derived from less than 2 oz raw liver Since ½ lb raw liver is the usual minimal daily quantity necessary to produce a satisfactory response in pernicious anemia it would seem that proteolyzed liver is relatively much more effective

It is also possible that various factors present in proteolyzed liver in addition to the liver principle of Castle may render this preparation of value in certain anemias associated with normoblastic bone marrow

[It should be emphasized that advocacy of oral preparations of liver in the treatment of certain macrocytic anemias must not be allowed to obscure the fact that ordinarily the active hemopoietic principle or principles of liver are from 60 to 100 times as effective by injection as by mouth Proteolyzed liver may be a useful accessory to the use of parenteral therapy in certain types of macrocytic anemia However the greater potency of proteolyzed or autolyzed liver over the original fresh liver or for convenience

Woman 67 presented a typical picture of pernicious anemia hemoglobin 49 per cent erythrocytes 1 650 000 color index 1 48 CV 24 per cent mean corpuscular volume 145 cu μ mean diameter 8.5 μ reticulocytes less than 1/1 000 white cells 5 400 There was a shift to the right in the Arneth count Erythrocytes showed anisocytosis poikilocytosis and basophilic stippling The indirect van den Bergh reaction was faintly positive A fractional test meal showed no free hydrochloric acid

Use of a liver extract of unknown potency was followed by no appreciable reticulocyte response and no rise in erythrocytes The blood also failed to respond to liver extract of



F g 47 —C e 1 Blood po se t p enter 11 xt ct f kn wn pot cy (PLE) d vit m n C

known potency The response to vitamin C in addition to liver extract is shown in Figure 48 Blood studies one month after discharge revealed hemoglobin 73 per cent erythrocytes 3 840 000 color index 0 95

During the same period many other patients with pernicious anemia exhibited progressive fall in erythrocyte counts despite the usual maintenance dosage of liver After receiving 100 mg vitamin C daily for one month without increase in the maintenance dose of liver extract all these patients showed a rapid increase of up to 1 000 000 red cells per cu mm with corresponding improvement in general health demonstrating that in pernicious anemia even with ample dosage of the antianemic principle hemopoiesis cannot be returned to normal when concomitant vitamin C deficiency exists

strongly positive Desensitization was begun with a dose of 0 1 cc liver extract, which was tolerated well increment of 0 1 cc were made at each successive dose, given every second day until a dose of 1 cc was reached, thereafter an increment of 0 2 cc was used The patient came every third day and remained in the hospital for two hours after each injection until he could tolerate 3 cc in one dose This do e was increased by 0 5 cc at two week intervals until 4 cc could be given in a single injection The patient now tolerates this dose every four or five weeks and with it maintains a normal blood picture *On some occasions after injection of 4 cc* liver extract he complains of slight headache and shows some swelling of the forehead this disappears after ephedrine is taken. The intradermal tests with liver extract are still strongly positive, though less so than before desensitization

CASE 3 —Woman 44, had been treated for pernicious anemia since August 1940, receiving 2 cc liver extract parenterally every two months In May 1941 after her usual injection he developed generalized urticaria and collapsed On three more occasions she developed urticaria after her injection In January 1942 intradermal tests with liver extract were strongly positive Because this patient has been unable to come to the hospital frequently, no serious attempt at desensitization has been made She is seen every six weeks and receives her requirement of liver extract in divided doses, starting at 0.1 cc with increments of 0 1 cc at 20 minute intervals until the first signs of intolerance appear these consist of flushing of the face and a feeling of tightness of the throat and usually appear after a single dose of 0 3 to 0 4 cc Dosage is then deferred until the following day when it is resumed at the level reached on the first day and proceeds at 0 2 cc increments at 20 minute intervals The full requirement of 4 cc for six weeks is usually injected in two days

It is emphasized that skin tests cannot be relied on to indicate tolerance in these cases for in Case 2 (not reported here) these were negative

Vitamin C Deficiency in Irresponsive Pernicious Anemia S C Dyke B L Della Vida and Elizabeth Delikat[7] report cases of pernicious anemia proving wholly or relatively unresponsive to liver treatment in which various considerations suggested that this was due to vitamin C deficiency Adjuvant treatment with ascorbic acid confirmed it Case 2 is reported here

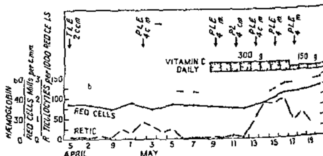
(7) Lancet 78 Sept 5 194

When the neurologic disorders which may precede accompany or follow onset of pernicious anemia are considered subacute combined system disease invariably comes to mind There can be little question that sclerosis and degeneration within the posterior and lateral columns of the spinal cord have been the most frequently observed pathologic findings The commonest clinical findings related to the nervous system in patients with pernicious anemia are paresthesia and dysesthesia of the feet and hands and impairment of vibratory and position sense particularly in the feet It is generally believed that the clinical findings are to be explained on the basis of the degree and location of the neuropathologic changes The actual cause of these changes is still a problem since there are a number of clinical conditions which may give rise to similar findings in the spinal cord Recently vitamin deficiency has been thought to play a part in producing these changes but it would seem in most cases that there is a combination of factors

Observations indicate that the degree of sclerosis in the posterior and lateral columns of the spinal cord does not always parallel the severity of the clinical symptoms and conversely that the patient may have severe subjective changes and yet have little to explain these symptoms on pathologic examination of the spinal cord This suggested that the peripheral nerves may be the source of certain clinical symptoms and signs and subsequent clinical investigation disclosed the presence of peripheral nerve disease in many patients with pernicious anemia who have neurologic complications

Generally the clinical diagnosis of peripheral neuritis is made on the basis of peripheral nerve pain dysesthesia or paresthesia tenderness on pressure over the nerve trunks or muscles usually with evidence of some muscle weakness as the disorder progresses and a loss or diminution of tendon reflexes starting distally There is also a tendency to distal superficial hypesthesia to pain and touch There is little diagnostic difficulty in severe cases

[A conclusion which while theoretically possible is not n e s-sarily supported by the evidence presented Referring to Figure 48 we see that a reticulocyte response and increase of red blood cells and hemoglobin occurred beginning four days after vitamin C administration was started *but also four days after parenteral administration of liver extract PLE 4 cc every other day was begun* It is therefore just as likely that the response is due to the latter as to the vitamin C That the response was entirely due to the PLE is strongly suggested by the data on Case 1 (see Figure 47) in which eight days after parenteral admin strat of 6 cc PLE (on the first and third days) a reticulocyte re sponse of 10 per cent had already been observed When more PLE was given on the seventh, tenth, twelfth and fourteenth



Fg 48 – Ca e

days the reticulocytes ro to about 0 per cent on the el v nth day *which was only three days after administration of vitamin C had been started* The data on Case 3 (not given here) indicate that vitamin C was given throughout the period of observation *but PLE was also giv n in 6 and 4 cc doses on the secon l and fifth days befor the peak* of reticulocyte response on the seventh day The best conclusion therefore that could have been drawn from these ob ervations was no conclusion at least as to the effectiveness of vitamin C in pernicious anemia Our confi dence in improvem nt reported as due to vitamin C therapy in the many other ca es not presented here is not enhanced by the analysis of the d ta on those that are presented —Eds]

Peripheral Neuritis as a Complication of Pernicious Anemia John B Dynes and John W Norcross[8] (Lahey Clinic) report on 92 cases of pernicious anemia 23 per cent presented clinical evidence of peripheral neuritis and combined system disease 24 per cent combined sys tem disease without peripheral neuritis and 53 per cent pernicious anemia without neurologic signs or symptoms

(8) J A M A 1 586 88 Ju e 6 1943

were no gross changes in visual fields or skull although the pituitary fossa was small Excretion of 17 ketosteroids was less than 3 mg daily The endocrine lesion was diagnosed as atrophy or hypofunction of the anterior pituitary lobe The presenting complaint was severe addisonian anemia—red cells 1 710 000 hemoglobin 38 per cent color index 1 1 leukocyte 9 000 differential count normal serum bilirubin 2 4 mg per cent and achlorhydria Liver therapy evoked a classic reticulocyte crisis and hemoglobin rose rapidly to 80 per cent

The association of pernicious anemia with hyperthyroidism pregnancy and pituitary disease suggests a hormonal element or mechanism which can lead to degeneration of the cells which secrete the intrinsic factor The incidence of pernicious anemia increases with age and from a wider biologic viewpoint the association of pernicious anemia with hypopituitarism may be considered another example of the precocious senile changes to which the patient with pituitary disease is susceptible Practically it is useful to remember that some of the physical and nervous symptoms of pituitary disease may in rare instances be due to an associated pernicious anemia and be relieved by liver therapy

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HYPOCHROMIC ANEMIAS

Hemoglobin Production Factors in Human Liver Anemias Hypoproteinemia Cirrhosis Pigment Abnormalities and Pregnancy G H Whipple and F S Robscheit Robbins[1] (Univ of Rochester) studied hemoglobin production factors in normal and abnormal human livers to devise better therapy in human disease Standardized dogs made anemic by bleeding were used for biologic assay Normal animal liver as control is rated at 100 per cent Normal human liver compared with normal animal control contains more hemoglobin production factors—a biologic assay ratio of 120 to 160 per cent Acute and chronic infections do not appear to modify these values

(1) J E p M d 6 83 98 S pt b 194

of peripheral neuritis, but if the disorder is milder or has been present sometime in the past, the acute signs and symptoms may have diminished greatly, and fewer diagnostic criteria are therefore available

The authors treat patients with severe neurologic complications with 20 U S P units (3 3 U S P units per cc) of liver extract intramuscularly daily for several weeks and then continue this dose every second day for several months Thereafter 20 U S P units should be administered at least twice weekly until the neurologic manifestations have improved or cleared The amount of liver extract needed varies considerably with the patient. The resumption of normal blood values may occur before any sign of improvement in the normal picture has occurred Large doses of vitamin B complex are always given by the authors as supplemental therapy

Pernicious Anemia and Pituitary Insufficiency Two cases are described by L J Witts[9] (Oxford Univ)

CASE 1 —Man, 58, had bitemporal hemianopia and pernicious anemia for two years He had unilateral cryptorchidism and had not married until 46, the union being sterile Personality structure was that of hypopituitarism The skin was lemon yellow and smooth and the hair thin and silky Roentgenograms disclosed an enormous pituitary fossa with an intrasellar fleck of calcification There were achlorhydria and anemia of high color index with a Price Jones curve at the extreme right of the normal range Basal metabolism was normal Despite treatment with liver the erythrocyte count at first fell and reached its lowest level—2 730 000 Hemoglobin was 66 per cent, color index 1 2 and leukocyte count 6,000 Smears of the sternal marrow at this time were identical with the peripheral blood A large internal hemorrhoid, from which there had been streaky bleeding was treated by phenol in oil injection Thereafter he responded well to liver red cell count rose rapidly to 4 230 000 and hemoglobin to 96 per cent

CASE 2 —Wizened woman 44, presenting an almost simian appearance looked much older than her age although her hair was still black She had never menstruated genitalia were small and underdeveloped and breasts and nipples were pre pubertal Basal metabolic rate was within normal limits There

(9) Lancet 2 30 308 Sept 1 194?

cythemia shows low biologic assay and subnormal iron store suggesting that iron and other hemoglobin producing factors are turned over rapidly to form new erythrocytes Overabsorption of red cell and hemoglobin producing factors appears responsible for this disease picture Leukemia presents a wide range of values which can be explained in various ways Loss of blood is often a factor in leukemia but iron stores are normal or above indicating that bleeding is not a serious drain on liver stores Marrow may be so choked with leukocytes that it produces too few erythrocytes and anemia results Meanwhile stores of iron and hemoglobin producing factor may heap up in the liver Leukocyte infiltration of the liver and associated degeneration may militate against storage of protein hemoglobin producing factors Iron stores are 3 20 times normal

Hepatitis with jaundice often shows low stores of iron and protein hemoglobin producing factors Low protein stores and hypoproteinemia favor liver injury—a vicious circle—as liver injury tends to slow up protein production Correction of this state is desirable and if protein cannot be given orally plasma protein can be given intravenously or intraperitoneally Methionine is specific against liver injury due to certain poisons and deserves a clinical test when continuing liver injury is suspected Protein orally or plasma intravenously also furnishes material needed for prompt repair of injured liver or other tissues

Hypochromic Anemia Following Gastric Pesection is discussed by G Hemmeler (Univ of Lausanne) on the basis of observations on patients who underwent gastric resection between 1935 and 1941 One group consisted of women of menstruating age Almost all of these developed iron deficiency anemia after operation The rapidity with which the anemia appeared depended on many factors state of the blood and iron reserves before resection amount of blood lost at operation ability

( ) S hw m d W h h 7 1105 1107 Oct 3 194

In pernicious anemia there is an average ratio of 243 per cent of hemoglobin building factors Substance X (present in liver extracts, liver stomach and kidney tissue) is lacking and unused substances pile up in reserve When liver therapy is effective these liver stores decrease to normal and ratios close to normal are observed as new erythrocytes form in great numbers In aplastic anemia there are also large liver stores of iron and hemoglobin production factors The liver probably stores these factors because bone marrow is aplastic and unable to use the stored material In secondary anemia exceedingly low iron stores and low normal or subnormal store of hemoglobin producing factor are found.

With hypoproteinemia the average ratio of normal human content of hemoglobin production factor is about 40 per cent Normal iron value for this type of human material is 12 mg per cent Therefore strong indication exists that protein factors (perhaps precursors of globin) are depleted by hypoproteinemia, whether associated with hepatitis or not The clinician views hypoproteinemia with disfavor for good reason When not sufficient to produce edema it may lower defense against infection and favor toxic liver injury

Iron and protein stores are low in late pregnancy due largely to fetal demands and needs for protein in lactation deplete hepatic protein stores which otherwise should go for plasma protein or hemoglobin These facts should direct attention to adequate intake of protein and iron in late pregnancy and during lactation Serious depletion of body protein reserves may be a precipitating factor in eclampsia Severity of depletion may determine whether eclampsia does or does not present widespread hyaline liver necrosis

Heavy iron deposits and approximately normal content of hemoglobin building factors are found in hemochromatosis erythroblastic anemia and hemolytic icterus suggesting that in disturbed pigment metabolism iron is the compound not readily available for absorption Poly

ally to 0 5 In many cases low serum iron level was the first manifestation presented by the anemia

Curves of iron absorption as indicated by serum content 2 4 6 and 10 hours after ingestion of 1 Gm reduced iron were determined for patients who had had gastric resection and compared with results in normal persons The serum iron level of the former was extremely low compared with that of the latter ranging from 60 to 100 mg with no appreciable increase after oral ingestion of reduced iron In normal subjects there was a sharp increase in blood iron from a resting level above 100 mg to over 250 mg four hours after ingestion with gradual decline of the curve thereafter When hydrochloric acid was administered in addition there was but slight response in serum iron curves of patients with resection When iron was administered in a special preparation of absorbable iron in the form of a ferrou salt combined with ascorbic acid (ferro redoxon) response of patients with resection was normal

Hemmeler concludes that anacidity or hypacidity of the gastric juice diminishes ionization of ingested iron a condition indispensable for absorption The rapidity of gastric movement also plays a role for the iron even when hydrochloric acid is present does not have sufficient time to ionize That the digestive contents do not pass through the duodenum is of no importance in the pathogenesis of anemia after gastric resection because ionized iron can be absorbed outside the duodenum Appearance of hypochromic anemia after resection can be minimized if proper precautions are taken including careful follow up study after operation with the la tory studies necessary to determine the import tors

Anemia in Women and Children on

Helen M M Mackay R H Dobbs Lucy Kaitilin Bingham[3] conducted hemoglobin on 1 074 persons comprising 364 children

(3) Lan t 2 3 33 July 11 1942

to absorb ingested iron and amount of blood usually lost during menstruation It is obvious that a subject anemic before resection will acquire hypochromic anemia early and will not be able to compensate it without treatment The size of the resected segment also plays a role If the remaining portion of the stomach is able to secrete sufficient hydrochloric acid to ionize the digested iron to render it absorbable, the anemia will be delayed Ionization can only take place in the stomach since the alkaline medium in the small intestine prevents transformation of alimentary iron into a bivalent absorbable form If a woman with a resected stomach is pregnant, she is bound to become anemic early because of giving her iron to the fetus loss of blood during delivery and loss of iron during lactation If anemia existed before pregnancy the fetus will not receive sufficient iron and both the mother and child will have hypochromic anemia

Another group of patients had reached the menopause before operation The percentage of those who developed anemia was markedly less than in the other group *Males showed an even lower incidence of hypo* chromic anemia apparently because men have a larger iron reserve than women who during their reproductive life lose considerable blood through menstruation and pregnancy

Subjective complaints of the patients with hypochromic anemia included fatigue cardiac palpitations dyspnea and profuse perspiration on the slightest exertion These symptoms constituting the so called ferroprivous adynamia were first manifestations of the anemia Trophic disturbances appeared late after hemoglobin content was reduced to 50 These were frail and brittle nails and hair glossitis frequently of Hunter s type intolerance of spicy and acid foods and chilliness The blood picture was characteristic Hemoglobin content was reduced much more than the erythrocyte count erythrocytes were markedly hypochromic and there were aniso and poikilocytosis color index was low occasion

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Anemia in Women and Children on Wartime Diets Helen M M Mackay R H Dobbs Lucy Wills and Kaitilin Bingham[3] conducted hemoglobin estimations on 1 074 persons comprising 364 children aged 6 months

(3) L t 3 33 July 11 194

to 5 years, 128 school children aged 5 15 38 factory girls aged 14 18 and 544 women of 18 and over The last included 229 hospital nurses, 124 medical students 159 factory hands and 32 *housewives The nurses and medical* students fell into two groups The first, living at a London teaching hospital had a mean hemoglobin level of 90 6 per cent the second living at a base hospital in the country had a mean hemoglobin level of 84 1 per cent The women with the highest average hemoglobin level in this series—94 per cent—were factory workers in a small town near London The group of East End housewives had an average hemoglobin level of 89 6 per cent

There was a high incidence of anemia among children aged 6 months to 5 years the mean hemoglobin values being 75 4 per cent at 6 to 12 months 72 8 per cent at 1 to 2 years and 81 8 per cent at 4 to 5 years School children aged 5 13 years had an average hemoglobin level of about 80 per cent A group of adolescent girls aged 14 18 working in a factory had the highest hemoglobin values for any age group averaging 98 per cent

The authors believe that in all an iron deficiency conditioned and unconditioned was probably the primary factor causing the anemia but that deficient and ill balanced diets and the high incidence of infection among children in institutions increased the anemia produced by low iron intake They suggest that the present increase in anemia in women and children should be combated by educating the public concerning their special need to obtain a full share of iron containing foods including meat by extending schemes for supplementing the diet of school children and pregnant and nursing mothers and by the provision of an iron fortified milk

Hypochromic Anemia in Patients with Deficiency of Vitamin B Complex Evidence that vitamin B and iron metabolism are intimately related is not conclusive except for pyridoxine in experimental animals That vitamin B complex increases therapeutic effectiveness of

iron in man is unsupported Carl V Moore Virginia Minnich (Washington Univ) R W Vilter and T D Spies[4] (Univ of Cincinnati) studied the response to iron therapy with and without yeast in 32 patients with hypochromic anemia Niacin deficiency ariboflavinosis or multiple neuritis was also present and 15 had lesions

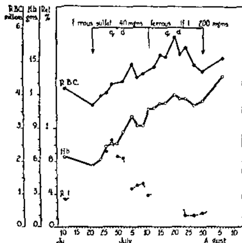


Fig 49—Response to iron therapy of patient with hypochromic anemia and deficiency ... multiple neuritis

of more than one type of deficiency disease The anemia showed no tendency to occur specifically in association with any of the three deficiency states No pyridoxine deficiency was found if present it was not accompanied by hypochromic anemia with high serum iron levels Three factors seemed to operate in producing the anemia chronic blood loss lowered gastric acidity and inadequate iron intake

Response to oral administration of iron alone was studied in 10 patients No other medication was permitted vitamins of the B complex were rigidly avoided and previous diets adhered to The usual therapeutic

(4) J A M A 1 245 50 J 23 1943

doses of ferrous salts were given (exsiccated ferrous sulfate 0 8 Gm daily) except in two cases in which the dose was limited to 0 16 Gm daily during the first 21 days A reticulocyte peak of 6 per cent or more was observed in each case 7 14 days after beginning iron therapy Five of six patients with initial hemoglobin value of 7 8 Gm or less showed a daily rise in hemoglobin of 0 13 to 0 22 Gm per 100 cc fever due to chronic pelvic infection was present in the sixth In four patients with initial hemoglobin above 7 8 Gm the daily rate of hemoglobin increase was 0 087 Gm or 5 565 per cent per 100 cc Oral administration of ferrous sulfate to these 10 subjects therefore was therapeutically effective in bringing about satisfactory hemoglobin regeneration Figure 49 shows one patient's response

During iron therapy lesions of the deficiency diseases usually remained relatively stationary after the observations were completed specific vitamin therapy with niacin riboflavin or thiamine never failed to correct them

While these observations prove that patients with hypochromic anemia and a concomitant deficiency of one or more vitamins of the B complex can absorb iron and utilize it effectively they do not eliminate the possibility that yeast might enhance the therapeutic response Four patients were given iron alone for 14 days and immediately thereafter iron supplemented with brewers yeast for an additional 14 days This was done for two reasons if the yeast increased the effectiveness of iron therapy (1) a second reticulocyte response should occur during *the second period and* (2) *the rate of hemoglobin regeneration* should be more prompt than when iron alone was given

Iron was given as 1 3 Gm ferrous gluconate daily Brewers yeast was administered in 25 Gm doses thrice daily No secondary reticulocyte rise developed following the addition of yeast and the average daily hemoglobin increase was no greater than when iron was given

alone The average rate for two subjects with initial hemoglobin values below 7 8 Gm was 0 17 Gm or 1 1 per cent per 100 cc daily for two with initial levels above 7 8 Gm 0 099 Gm or 0 064 per cent Brewers yeast therefore had no additive effect in promoting a more rapid hemopoietic response

[Here is evidence that for the treatment of hypochromic anemia even in the presence of manifest deficiency disease vitamin B complex components are not of value To add them to iron compounds for the treatment of anemia is to dilute (and expensively) the efficiency of the iron —Eds]

Iron Refractory Anemia in Hookworm Disease Robert Heilig and Visweswar⁵ (Univ of Mysore) state that one of the most impressive experiences in clinical medicine is the improvement of anemia in ankylostomiasis when organic iron is supplied in sufficient quantities Increase in erythrocytes and hemoglobin often proceeds at a rate of half a million red blood cells and 10 per cent hemoglobin per week from the second week on To maintain this good condition complete deworming must follow the antianemic course No carbon tetrachloride or tetrachlorethylene should be given to a patient with a hemoglobin level below 40 per cent All dangers of hookworm destruction are avoided by strict observance of this rule

Woman 30 had received 500 liver injections for anemia of eight years duration Red cell count was 1 330 000 and the hemoglobin level 15 per cent The second stool examination in the hospital showed hookworm ova Bland s pills (90 gr per day) the only remedy given increased the red blood cell count to 3 250 000 and the hemoglobin content to 40 per cent in three weeks

Anemia due to ankylostomiasis improves quickly and regularly on iron medication *without additional treatment and before deworming is done* [editors italics] Any delay in achieving a favorable response must be traced to some other active pathologic process coexistent with the ankylostomiasis To determine which of the accompanying infections is responsible is of great im

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portance The only way to prevent further deterioration of the blood condition and thus save the patient is to eliminate the infection among the usually multiple infections which makes the anemia iron refractory In the authors' cases malaria urinary tract infections, silent otitis media and sinus affections usually were responsible for failure of the hookworm anemia to respond to iron In such cases the diseases should be treated simultaneously before negative response to iron is noted

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OTHER ANEMIAS

The following articles are concerned with certain anemias not covered in the preceding sections —Eds

Sternal Marrow in Banti s Syndrome and Other Splenomegalic States together with observations following splenectomy is discussed by Louis R Limarzi Robert M Jones Jerome T Paul and Henry G Poncher[6] (Univ of Illinois) Twenty one patients with Banti s syndrome presenting marked variation in individual findings were studied and 10 persons without clinical abnormalities were used as controls

Theories concerning the pathogenesis of Banti s syndrome can be divided between an infectious process as the causative agent and mechanical factors which produce the symptom complex as the result of obstruction to the portal blood flow

The anemia and leukopenia accompanying Banti s syndrome have been variously attributed to hemorrhage to a toxic process acting on the marrow and to suppression of bone marrow function by a hormone produced in the diseased spleen In the authors patients with Banti s symptom complex without cirrhosis the anemia granulopenia and myeloid immaturity with toxic changes in the granulocytes peripherally and hyperplasia with a 'maturation arrest of the granulopoietic tissue in the bone marrow seem to speak for a chronic, toxic process

(6) Am J Clin P th 13 231 248 May 1943

as the cause A factor which suppresses the normal de livery of the granulocytes from the marrow to the periph eral blood seems to be present When splenectomy has been performed in this group of cases the peripheral blood patterns except for the presence of Howell Jolly bodies have returned to normal while the bone marrow has remained hyperplastic Thrombocytosis and leuko cytosis with monocytosis and eosinophilia were rather constantly observed following splenectomy and in a few cases persisted indefinitely

When the syndrome has progressed to the stage in which there is marked cirrhosis of the liver the marrow shows a shift in erythrogenic tissue toward immaturity with a pronormoblastic state similar to that seen in atrophic cirrhosis of the liver It is interesting to note that the anemia present in the Banti s group studied at this stage has been normocytic in almost all cases while that accompanying atrophic cirrhosis has been macro cytic The results of splenectomy in the authors cases of Banti s syndrome with erythroid immaturity of the marrow have been poor

Familial Mediterranean Target Oval Cell Syndromes William Dameshek[7] (Tufts College) reports the study of 10 Italian families and of 1 Italian bachelor (com prising altogether more than 50 individuals) all affected with various syndromes presenting among other features target cells and increased hypotonic resistance of the erythrocytes These are believed to be a single condition but of varying degrees of intensity Brief resumes of these families follow

1 Caruso family—hypochromic anemia marked splenomegaly acholuric jaundice marked bone changes target oval and stippled red cells increased hypotonic resistance

2 Perriello family—hypochromic anemia spleno megaly no bone changes acholuric jaundice target oval and stippled red cells

(7) Am J M S 205 643 660 May 1943

3 Luccio family—hypochromic polycythemia, frequent splenomegaly occasional jaundice occasional heart murmurs reticulocytosis, target oval and stippled red cells no bone changes

4 Corrao family, Veneziano family Danubio (bachelor)—hypochromic polycythemia without icterus splenomegaly or bone changes, target oval and stippled cells increased hypotonic resistance



Fig 50—Bl d sme of ase f outspoken Cooley s anem a p r t splene t my G t d e s ty in cell s e w th both microsph ytes nd macrocytes an as l nu leated red cell and an occ s on l ta g t cell m ked e d n e f bl d d t u tion p es nt

5 Mariello family—mild refractory hypochromic anemia without icterus or splenomegaly and with target, oval and stippled red cells

6 Unselected Italian individuals (60)—in 8 (13 per cent) definite changes such as target, oval and stippled cells

The fundamental unity of the various target cell syndromes including Cooley's anemia is evident from this study This is indicated by the following observations (1) Certain siblings and both parents of the patients with Cooley s anemia showed the hematologic changes of the mild Mediterranean target cell syndrome usually hypochromic polycythemia (2) The various groups merged into each other by insensible transitions (3) Individuals of the same families occasionally showed the same variations as were noted in the groups These considerations indicate that Cooley s anemia (Fig 50) is probably the most severe manifestation of a heredi

tary disorder occurring in people of Mediterranean origin and in which target cells and increased hypotonic resistance are prominent features

In the families in which one of the milder syndromes (Fig 51) was present inheritance was present as a simple dominant mechanism occurring through either parent This is well brought out in the Perriello Luccio and Veneziano families in which members of three generations were studied Seven of the eight Perriello children and four of the five Luccio children were affected although in different degrees In the Perriello family the transmittor was evidently the grandmother who showed *a mild condition of hypochromic anemia with elliptic and target cells Her daughter showed a much* more severe condition with jaundice and splenomegaly and the latter s children were similarly affected The male grandparent and parent were both completely normal In the Luccio family the grandmother son and the latter s children all showed hypochromic polycythemia with target oval and stippled cells the grandfather and



Fig 51—Bl d m f f hyp h m n m (M ll) with t g t nd oval cell

the daughter in law however, were both found normal

In the families of the four patients with severe cases—three with typical Cooley's anemia and one with the 'anerythroblastic type—both the father and the mother showed a mild target oval cell syndrome What is more, a mild Mediterranean disorder was often present in certain of the siblings of the patients with Cooley's anemia This suggests that the mild disorder is readily transmitted as a mendelian dominant, but that the severe disorder requires the presence of homozygous genes The exact nature of the hereditary process remains to be worked out

The hypochromia the low mean corpuscular volume and the complete lack of response to iron medication suggest a disturbance in the hemoglobin metabolism more particularly perhaps in the development of a normal complement of hemoglobin in the cytoplasm of the nucleated red cells in the bone marrow This may be reflected by the development of unusually thin mature red blood cells (target cells and oval cells) Red cell formation is itself probably undisturbed since there is erythroblastic hyperplasia of a normal (normoblastic) type and the red cell count in the peripheral blood is frequently greater than normal The presence of large numbers of stippled red cells suggests a possible 'toxic effect on the developing red cell, however this seems unlikely in view of the hereditary nature of the process and may be further evidence of an abnormal hemoglobin metabolism Of interest in the more severe cases is the presence of increased hemolysis of which the cause is at present obscure This may be due (1) to an increased breakdown of hemoglobin precursors which cannot properly be metabolized (2) to a possible increased in vivo fragility of the target cell although in vitro it has an increased resistance to hypotonic salt solutions or (3) to some abnormality of the spleen Combinations of these factors are also possible Coincidentally with increased blood destruction are certain evidences of increased

blood regeneration reticulocytosis leukocytosis in some cases and perhaps basophilic stippling The high red cell counts in many of the cases suggest an attempt on the part of the marrow to compensate for the hemoglobin deficiency All that can be stated is that the disorder—whether mild moderate or severe—is an inherited one in which the red cells are abnormally thin (leptocytosis) and the hemoglobin production abnormal

Familial Blood Studies in Cases of Mediterranean (Cooley's) Anemia are reported by Carl H Smith[8] (Cornell Univ) In 16 families with Mediterranean anemia 54 of 63 persons examined revealed blood ab normalities Twelve all children were severely anemic and 42 including parents and siblings had the mild type of this condition In all the 16 families definite blood changes occurred in at least one parent and in 1 family changes were noted in three generations

All available siblings and parents of patients with Mediterranean anemia were examined clinically hema tologically and roentgenographically Persons with the mild form of the disease were asymptomatic and recog nition depended solely on careful blood study The changes consisted of varying degrees of hypochromic anemia occasionally polycythemia an elevated icteric index presence of target cells reticulocytes macrocytes and stippled red cells and increased resistance of the red cells to hemolysis The commonest findings regard less of the severity of the anemia were anisocytosis and poikilocytosis basophilic stippling and increased resist ance to hypotonic solution of sodium chloride Hypo chromic and polychromatophilic macrocytes constituted an important diagnostic feature and were frequently found in predominantly microcytic blood smears

Target cells appeared in only half the patients with mild forms of the disease Target corpuscles are non specific cells and there appears to be no justification for designating any anemia by their presence Thinness

(8) Am J Dis Child 65 681 701 M y 1943

and flatness of the cells on the other hand may represent the fundamental structural defect of the erythrocytes in Mediterranean anemia This quality was inferred from their resistance to hemolysis in hypotonic solutions of sodium chloride and by direct examination of wet and stained smears

The degree of skeletal change was usually correlated with the severity of the anemia In affected parents bone changes were usually *absent or equivocal* In children with mild forms of the disease minimal bone involvement was noted The earlier the onset, the more severe the anemia and the more extensive the skeletal changes *The later in childhood the disease became manifest,* the less severe was the osteoporosis In the milder form osteosclerosis tends to obliterate evidences of minimal degrees of decalcification Therefore in older children *and in adults with mild forms of the disease no significant* roentgen changes can be expected

In every family with a severely anemic child both parents showed abnormalities of the blood Although this happened in six families it cannot be regarded as invariable

The data suggest that certain features of the blood in Mediterranean anemia may be said to represent a trait similar to traits already established for sickle cell anemia and to a more limited degree for congenital hemolytic jaundice The evidence for existence of the trait in Mediterranean anemia depends on identification of a number of abnormalities in the blood smear and of a prolonged fragility span since there is no single cell that may as yet be regarded as specific for Mediterranean anemia The fact that Mediterranean anemia of all grades of severity proves refractory to treatment often aids in its diagnosis particularly of the milder form and this is further corroborated by discovery of the familial incidence of the anemia.

The children of a parent with the trait run the risk of inheriting the disease in any of its clinical forms

from the mildest to the most severe Since the disease appears to be transmitted directly from parent to child the implications of the existence of mild forms of Mediterranean anemia are obvious in communities with large Italian and Greek populations This study suggests that the trait is transmitted as a dominant characteristic

The prognosis of Mediterranean anemia depends on the fact that the disease manifests a continuous range of variation from the mildest form represented by the trait to the advanced types marked by severe anemia. The evidence supports the view that the advanced and well recognized form of Cooley's anemia represents a severe and often fatal form of a more widespread disease of variable intensity

Indications for Splenectomy in Gaucher s Splenomegaly Abraham O Wilensky[9] (New York City) states that repeated episodes of minimal or maximal hemorrhage in association with splenomegaly usually result from a hematologic abnormality occurring either as an independent pathologic entity or as a symptomatic manifestation of another form of disease In the first group splenectomy is a curative measure (1) in the forms of hemolytic icterus in which the circulating blood contains spherocytes or (2) in cases of thrombocytopenic purpura [sometimes—Eds] In the second group splenectomy is valuable for cases (3) in which excessive enlargement of the spleen becomes a physical handicap and leads to cachectic states and (4) in which repeated or massive hemorrhage occurs because of accompanying thrombocytopenic manifestations Both of the last two conditions are encountered in Gaucher s splenomegaly and demand splenectomy as a palliative therapeutic measure performed if possible during a so called remission period

Gaucher s disease is a form of general lipidosis produced by accumulation of kerasin in the reticular cells and histiocytes of the lymph hemopoietic organs The

(9) J M Soc New Jers y 39 31 537 Octobe 194

typical large swollen, pale grayish white translucent Gaucher cell occurs in striplike accumulations in such amounts as to produce marked enlargement of the spleen liver and deep lymphatics and defects in the marrow of the long bones

In the usual chronic case there is indefinite symptomatology characterized by various pains and aches, weakness and inability to carry on customary routine Commonly the first complaint is progressive abdominal enlargement In others the chief complaint is recurrent hemorrhage or hemorrhagic diathesis Another group comes with dragging pains in the thighs (femora) or back (spine) commonly mistaken for osteomyelitis or arthritis as bouts of fever are common the similarity is marked

Diagnosis is based on enlargement of the spleen liver and deep lymph nodes skeletal defects skin pigmentation cuneiform yellowish or brownish conjunctival thickenings near the cornea hemorrhagic tendencies due to thrombocytopenia leukopenia microcytic anemia and general emaciation in advanced stages *Of these the most* important are splenomegaly and conjunctival and bone changes

Wilensky describes two cases The first illustrates the course of a typical long standing chronic case including bone manifestations and mistaken initial diagnosis of osteomyelitis and later repeated hemorrhages The second shows the effect of thrombocytopenia in evoking hemorrhagic diathesis

Familial Idiopathic Methemoglobinemia James Deeny Eric T Murdock and John J Rogan[1] report results of ascorbic acid treatment in two cases

CASE 1—Man 29 livid blue since birth, felt moderately well but experienced dyspnea on exertion and was constipated He could not exercise strenuously and noted that his condition was more severe in cold weather A diagnosis of methemoglobinemia had been established by spectroscopic blood examination The skin of the face, including the ears

(1) Brit M J 1 7 1 723 June 12 1943

and neck, the hands, feet, mucous membranes and to a lesser extent the trunk were a deep bluish color In contrast to the cyanosis usually found there was no underlying reddish tint The heart was normal in size and without valvular defects Blood pressure was 140/90 the erythrocyte count was 5 900 000 The oxygen combining capacity of the blood was 13.2 volumes per 100 cc (normal, approximately 20 volumes per 100 cc) The spleen was not palpable

He was given 50 mg ascorbic acid night and morning on the first day then 100 mg similarly the next two days followed by 150 mg twice daily thereafter Two drachms sodium bicarbonate was given each day at noon to elevate the renal threshold for ascorbic acid On the eighth day when he had taken a total of 2 Gm ascorbic acid a sudden and noticeable change occurred in his color and on the twelfth day his complexion became natural Since then he has continued with 300 mg ascorbic acid and 1 drachm sodium bicarbonate daily and has remained normal in appearance The ascorbic acid was given in graduated doses as it was uncertain what might result from any possible rapid increase in available oxygen In this respect the only significant feature was a sudden attack of vertigo on the third day of treatment which lasted for 30 minutes but passed without ill effect After one month the oxygen-combining capacity of the blood was 22 volumes per 100 cc On the sixty third day of treatment the blood ascorbic acid was 1.55 mg per 100 cc there was 11 per cent methemoglobin (sulfhemoglobin absent) erythrocytes numbered 5 080 000 and there was 0.5 per cent reticulocytes

CASE 2—Brother of the patient in Case 1 had milder methemoglobinemia Treatment with ascorbic acid and sodium bicarbonate was equally effective

The relationship of ascorbic acid to hemopoiesis in man is not clear Dunlop and Scarborough showed that a rise in the number of red cells a fall in reticulocytes and an increase in hemoglobin followed ascorbic acid therapy in a patient with scurvy although the iron content of the diet remained unchanged Barron and Barron observed that ascorbic acid reduced the red cell count in rabbits with cobalt induced polycythemia It was thought that polycythemia is caused by inhibition of the respiration of immature red blood cells and their expulsion from the bone marrow into the circulation as mature nonrespiring cells Kandel and LeRoy treated two

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(1) B t M J 1 7 1723 Jun 1 1943

portal circulation in the liver as the result of the increased blood volume (2) stasis of blood flow caused by increased blood viscosity and in some cases by development of cardiac failure (3) increased strain on hepatic function due to the excessive hemolysis that occurs with phenylhydrazine treatment and (4) impairment of nutrition of the hepatic cells as a result of the stasis of blood flow

Some reports state that splenomegaly occurs in 75 per cent of cases of polycythemia vera Splenic infarcts hemorrhages and perisplenitis are not uncommon Among the 163 cases of polycythemia vera studied there were 107 in which the spleen was easily palpable In 17 of these it was enlarged to the umbilicus and in 13 it was felt midway between the costal margin and the umbilicus In 21 cases it was merely mentioned as palpable Seventeen patients had pain in the left upper abdominal quadrant or were able to feel the spleen and mentioned this as one of their chief complaints None of these patients had received phenylhydrazine In seven cases the chief complaint was referable to the spleen. A clinical diagnosis of splenic infarct or perisplenitis was made in 11 cases 9 before treatment with phenylhydrazine and 2 after treatment In many of these cases the size of the spleen varied from time to time particularly in cases in which splenic infarct or perisplenitis was suspected clinically The enlarged spleen was usually smooth and firm and frequently tender In one case it was nodular In two cases the spleen was so large and tender that splenectomy for symptomatic relief was considered

In 15 cases in which the spleen was excessively large a leukemoid reaction was found in 5 of these cases it was so marked that the blood smears closely simulated those in myelogenous leukemia Four of the five patients lived for long periods 12 15 20 and 23 years respectively after the diagnosis of polycythemia had been made In seven cases in which the spleen was exceedingly

patients with polycythemia vera with large doses of ascorbic acid without altering the red cell count or hemoglobin level Deeny however caused clinical improvement in two cases of polycythemia with ascorbic acid therapy after first raising the renal threshold for ascorbic acid by giving sodium bicarbonate The results in these cases led to the present investigation the results of which confirm the findings of Lian Frumusan and Sassier that administration of ascorbic acid diminishes cyanosis and methemoglobinemia

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POLYCYTHEMIA

Liver and Spleen in Polycythemia Vera W S Tinney B E Hall and H Z Giffin[2] found some hepatic complication in 40 of 163 cases of polycythemia vera studied In 31, the liver was palpable half way to the umbilicus and in 1 case it was palpable at the umbilicus Bromsulfalein tests demonstrated dye retention in nine cases A definite clinical diagnosis of hepatic cirrhosis was made in five cases and in two others a diagnosis of hepatic damage was made In three of the cases of cirrhosis severe and repeated hemorrhagic manifestations occurred, these were usually in the form of purpura, hematuria or hemorrhage after minor surgery Two of the patients with hepatic damage had gout *Ascites was demonstrable in six cases and marked* jaundice in three before treatment with phenylhydrazine A clinical diagnosis of portal thrombosis was made in six cases but was proved by necropsy or operation in only two

Among the many vascular complications of polycythemia vera those of the intra abdominal vessels are frequent particularly those involving the portal vein Moreover, in this disease hepatic function may be impaired by at least four known factors (1) distention of the

(2) Proc. Staff Meet Mayo Clin 18 46-48 Feb 10 1943

ized and obvious glandular enlargement others have no apparent involvement and between these extremes lies every variation The commonest site of enlargement is the cervical glands especially those in the posterior triangle After first appearing at this site enlargement may involve other groups or it may appear first in the inguinal or axillary glands with later appearance of cervical swellings Degree of enlargement likewise varies but the diameter is commonly less than 2 cm The glands are usually ovoid and rubbery Occurring singly or in groups but always discrete they are generally mobile and may be painful on pressure

Splenomegaly is common Skin eruptions are infrequent said to occur between the fourth and the tenth day they are most frequently of the typhoid variety but morbilliform scarlatiniform urticarial and vesicular eruptions have been described

Positive diagnostic evidence is gained only by examination of the blood cells and serum Changes in number and type of leukocytes are unique development of an absolute lymphocytosis is the most characteristic feature but other leukocytes are affected also In most cases the leukocytes number 5 000 15 000 per cu mm The blood count of children over 7 is usually the same as that of adults but in infants the leukocytosis may exceed 40 000 per cu mm An early neutrophilic leukocytosis may prelude the typical mononucleosis

Mononucleosis may appear in the earliest period but it generally evolves during the first 4 days and becomes maximal within 10 days Most cases present mononucleosis of 60 to 90 per cent but diagnosis is more dependent on the type of cells found than on their numbers The mononuclear agranulocytes are of three main types normal lymphocytes normal monocytes and abnormal mononuclear cells The last vary in size from that of a small lymphocyte to that of a monocyte The nucleus whose relative size is variable may be circular reniform or indented it usually stains darkly but not evenly The

large a leukemoid reaction was not present Engorgement of the spleen with blood is an important factor in the splenomegaly as well as in the hepatomegaly of polycythemia vera When the blood counts and the percentage of cells as indicated by the hematocrit readings are reduced by treatment, the spleen may decrease in size

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INFECTIOUS MONONUCLEOSIS

Infectious Mononucleosis Problem in Diagnosis T E Hester Spark[3] (Sydney) defines infectious mononucleosis as essentially a disease of children and young adults Incubation period is unknown but 11 days is considered likely There is no typical mode of onset, every variety of symptom may be found from the most insidious to the most fulminant The slow onset is characterized by vague constitutional disturbances, such as malaise nausea and anorexia Symptoms referable to the throat occur in most patients in the earlier stages of infection Extent of throat involvement varies from slight pharyngitis with mild dysphagia to acute ulcerating lesions, with membrane formation suppuration and sloughs *Abdominal pain* has been noted by some

Fever is probably the most consistent feature It usually appears suddenly and with daily increments reaches a peak in three to four days Frequently it is of the remittent form with evening rises and subsequently subsides within two to four weeks A rather typical feature of the febrile reaction is the secondary rise in temperature after a return to normal associated with generalized glandular involvement The pulse rate is usually increased in direct proportion to the temperature, but in some cases bradycardia is present Temperatures as a rule do not reach high levels though in most cases at the maximum they exceed 102 F In occasional cases the course is entirely afebrile

Adenopathy is variable Some patients have general

(3) M J Australia 2 413-4 1 N 7 1942

though this is usually preceded by some form of drug therapy The mononucleosis of glandular fever can usually be distinguished from the neutrophilic leukocytosis of sepsis but the occasional case of mononucleosis in which an early granular leukocytosis occurs may cause confusion.

Secondary syphilis may be a source of error for it can cause other glandular enlargement than the well recognized suboccipital involvement and the bubo A further difficulty arises in the occurrence of a false positive Wassermann reaction in infectious mononucleosis Careful inquiry into the history and earliest symptoms will usually forestall this error

Lymphadenoma and lymphosarcoma also merit consideration for enlarged glands and splenomegaly occur in both In addition the febrile reaction of infectious mononucleosis may be misconstrued as an atypical Pel Ebstein phenomenon and so lead to an incorrect diagnosis of Hodgkin s disease However the insidious onset of symptoms in Hodgkin s disease should obviate mistakes

Acute leukemias of either lymphatic or monocytic type may constitute serious diagnostic problems They may have the acute onset with pyrexia and glandular enlargement which are so suggestive of infectious mononucleosis and even examination of the blood film may be deceptive Hemorrhagic phenomena and anemia are the rule in acute leukemia whereas they are exceptional in infectious mononucleosis the most important point of differentiation is that in the leukemias a uniform type of immature cell is usually encountered whereas in infectious mononucleosis the predominant cell is of older type and more variable in its characteristics

Cases of infectious mononucleosis in which fever is the most conspicuous feature at times present the greatest difficulty The disease may closely simulate typhoid fever and in such cases the heterophil antibody test may provide the only conclusive diagnostic evidence Among

cytoplasm may be pale but is usually deeply basophilic and may be vacuolated or contain azurophil granules

The second conclusive diagnostic maneuver is the *Paul-Bunnell heterophil agglutination test* [See following article by Kilham and Steigman —Eds] The presence of the heterophil antibody in the serum of patients with infectious mononucleosis is demonstrated by its ability to agglutinate sheep s corpuscles Studies have shown that serum disease is the only other condition in which heterophil antibodies are found in dilutions greater than 1 16, and this condition sometimes gave a positive response to the test in a dilution of 1 64 Therefore when a patient's serum agglutinates sheep s corpuscles in a dilution greater than this figure, it may be concluded that the case is one of infectious mononucleosis *Agglutination* in dilutions up to 1 1 000 is the rule and cases have been reported in which agglutination occurred in a *dilution of 1 163,840*

False positive reactions to the Wassermann test are sometimes encountered When present they usually appear in the second week and are of short duration, lasting generally only a matter of days An incidence of 18 per cent has been recorded in one series

Cases in which glandular enlargement is conspicuous may cause difficulty in differentiation from many conditions especially when the cervical glands only are affected Of these sepsis is one of the commonest such as acute follicular tonsillitis However, infectious mononucleosis is commonly misdiagnosed as pharyngeal diphtheria for a pseudodiphtheric membrane is not unusual. Such erroneous diagnosis may lead to administration of antidiphtheric serum and should serum sickness subsequently develop confusion may be caused in the interpretation of the heterophil antibody test Vincent s infection is a common accompaniment of infectious mononucleosis and clinical signs of the former should always suggest the possibility of the coexistence of the latter Agranulocytosis is another possible cause of error

Onset was sudden in 3 patients and gradual in 17 Duration was 8 25 days Clinical improvement occurred in a few days in about one third of the cases but more gradually in the rest

Fatigue was commonly one of the first symptoms Sore throat headache and cervical lymphadenopathy occurred in most patients Cervical lymph nodes produced pain and stiffness of the neck in some Nausea and epigastric discomfort associated in one case with vomiting oc curred in four jaundiced patients and in only one non jaundiced Fifteen patients had fever of low grade or short duration 2 presented diurnal fluctuations between 99 and 103 F for 10 days and 2 had low grade fever for nearly two weeks One had sustained pyrexia of 102 103 F which fell by crisis after six days

Physical Findings—Rashes in five cases were of three types morbilliform scarlatiniform and erythema iris A morbilliform rash occurred in three cases with jaundice In two of these the rash appeared the seventh day and lasted three or four days in the other it ap peared the sixteenth day A transient brownish discolor ation remained Itching was slight The scarlatiniform rash occurring on the trunk and abdomen of one patient the sixth day faded in a few days The erythema iris rash developed in another patient the sixth day and persisted for 10 days

Seven patients presented hyperemic conjunctivas at some stage of their illness Two had palpebral edema one with extreme enlargement of cervical lymph nodes pos sibly due to pressure on the jugular veins

The oral mucosa presented petechiae in eight patients three with concomitant morbilliform rash and icterus one of whom had numerous petechiae in the mouth and hematuria but no additional hemorrhagic phenomena Tender irregular red papules 0 5 cm in diameter over the hard palate were discovered in one case on the fourteenth day and lasted three days

Enlarged tonsils occurred in 17 patients In two the

other causes of obscure pyrexia special attention should be paid to the likelihood of bacterial endocarditis, septicemia and local suppuration, especially perinephritic abscess All these conditions are associated with a neutrophilic leukocytosis which should suffice to differentiate them from infectious mononucleosis though such a blood finding occasionally occurs in the earliest stages of infectious mononucleosis

Also meriting reference are jaundice, mumps and the infective exanthemas Cases have been reported in which jaundice of obscure origin was found to be due to infectious mononucleosis The jaundice is of the regurgitant type and is thought to be due to enlargement of glands in the portal fissure This type of jaundice when occurring in the young is likely to be diagnosed as catarrhal jaundice In any such case if there is reason to doubt the diagnosis a blood film should be examined and the serum investigated for heterophil antibodies Mumps should not cause erroneous diagnosis for infectious mononucleosis does not affect the salivary glands Hematologic findings serve to differentiate infectious mononucleosis from rubella and scarlatina for all of these conditions may present skin manifestations glandular enlargement and pharyngitis

Prognosis is invariably good in infectious mononucleosis most patients recover completely in a few weeks Treatment is symptomatic Tonics or iron therapy may be desirable during convalescence Most patients however require only bed rest aperients and perhaps an aspirin phenacetin and caffeine mixture to relieve headache in the early stages

Infectious Mononucleosis Lawrence Kilham and Alex J Steigman[4] (American Red Cross Harvard Field Hosp Unit) review laboratory and clinical data on 20 cases, equally divided as to sex Sixteen patients were 18 25 age limits being 10 and 34 Seasonal variation in incidence was not evident

(4) La cet 2 45 -454 Oct 17 194

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tonsils met in the midline, causing considerable dysphagia An easily removed gray white membranous exudate covered the enlarged tonsils in 10 cases No membrane occurred without tonsillar enlargement Adenoid enlargement was suggested in four cases

Cervical lymph nodes particularly at angles of the jaw, were enlarged in all cases and often tender Axillary, epitrochlear and inguinal nodes were less constantly involved Enlargement regressed rapidly once general recovery set in

The spleen was palpable in 11 patients by the second week in all but one just below the costal margin The exception who had a tender splenic edge 3 fingerbreadths *below the costal cage also presented the sole instance* of hepatomegaly encountered

Seven patients had jaundice four with clinical jaundice and the others with laboratory evidence of subclinical icterus.

Laboratory Findings—Three types of heterophil antibodies found in human serum agglutinate sheep erythrocytes These are differentiated on the basis of absorption by ox erythrocytes or guinea pig kidney One type found in normal serum, is not absorbed by either reagent whereas the type found in human serum after horse serum injection is absorbed by both. In infectious mononucleosis the diagnostic heterophil antibodies are absorbed by ox erythrocytes but not by guinea pig kidney The Barrett modification of the Paul Bunnell test differentiates the three types By this test sheep cell agglutinins in a titer of 1 40 or above are considered diagnostic if they are absorbed by ox erythrocytes In this series all cases had a titer of 1 160 or higher except for a single titer of 1 80 Repeated tests in six cases disclosed that the titers rose during the second or third week. In two the sheep cell agglutination test was negative during the first week but repeated tests gave strongly positive results at the beginning of the third week. The serums of four patients had titers

reaching 1 2 560 two in the first week and two in the third No constant relationship existed between height of the titer and clinical severity of the illness One had a titer of 1 80 three months after onset of illness

Leukocytosis occurred in all cases at some time during the first two weeks with total leukocyte count of 10 000 or above Maximal leukocytosis occurred irregularly during the first three weeks with counts to 32 000 per cu mm

Two patients had initial leukopenia one with a total leukocyte count of 4 300 per cu mm the tenth day rising to 21 000 the nineteenth day Polymorphonuclear neutrophils in this case showed the greatest fall numbering 1 720 per cu mm the tenth day A second case was essentially similar

It has been suggested that the so called anginose type of infectious mononucleosis is due to granulocytopenia Nine patients had granulocyte counts below 2 000 per cu mm the lowest being 900 The two severest anginose cases had normal or slightly increased polymorphonuclear counts of 4 500 and 6 800 per cu mm All of these showed a relative or absolute decrease in polymorphonuclear neutrophils whereas in many instances the degree of secondary infection caused anticipation of considerable polymorphonuclear response Suppression of polymorphonuclears therefore appears to have been present

The percentage of mononuclear cells was 68 78 per cent as the maximum response All smears showed varying numbers of atypical lymphocytes The authors believe that no particular cell type is peculiar to or specifically diagnostic for infectious mononucleosis The chief characteristic of the atypical lymphocyte as stated by Bernstein is its variability Among the salient features common to many of the atypical lymphocytes were a deep and coarsely staining nucleus often showing fenestration and irregular shape The cells were all roughly the size of large lymphocytes

The van den Bergh reaction was direct in five patients all with bile in the urine Three with obvious jaundice had serum levels of bilirubin of 4 5 to 7 5 mg per cent, and a fourth with minimal jaundice had 1 4 mg per cent The fifth patient was deeply icteric the eleventh day cholesterol was 285 mg per cent, phosphatase 26 Bodansky units and bilirubin 1 5 mg per cent The low serum bilirubin was associated with fading icterus Liver biopsy in this case showed parenchymatous changes, sections showed well marked focal acute hepatitis Maximal change was observed in the portal tracts of the lobules with loss of liver cells and well developed histiocytic reaction with some early proliferation of bile ducts Isolated foci of similar histiocytic reaction existed in other parts of certain lobules and sinusoids showed an excess of cells some being Kupffer cells and others resembling monocytes Glycogen content of hepatic cells was well preserved and general appearances suggested that an earlier phase of necrosis had preceded the histiocytic reaction The reticular pattern of the lobules was disturbed in the affected portal zones but there was no true fibrosis

Bile was demonstrated in the urine of seven cases four of them clinically jaundiced One patient had hematuria throughout the third week with no indication that any other cause was responsible

Throat cultures from 12 patients demonstrated wide variation No one organism was common to any significant number

Lumbar punctures gave negative results in two of four patients One with distinct encephalitis evidenced by severe headache drowsiness nuchal rigidity and irrationality had 56 white cells per cu mm spinal fluid 80 per cent of which were lymphocytes protein and pressure were normal Another patient without meningeal signs or symptoms had 30 leukocytes per cu mm spinal fluid chiefly lymphocytes and normal protein and pressure

Sedimentation rate studied in four patients was within normal limits for three and slightly elevated for the fourth

TREATMENT —This was largely palliative Five patients with well marked pharyngeal involvement and streptococci in throat cultures received 30-40 Gm sulfadiazine in five to six days without demonstrable effect Sears suggested that sulfonamides might be h zardous because of frequent coexistence of granulocytopenia Of the five treated with sulfadiazine in the authors series two showed slight depression of polymorphonuclears while in two the number was elevated Scarlet fever convalescent serum was given in one case but the patient had already shown signs of recovery and no benefit could be ascribed to the serum

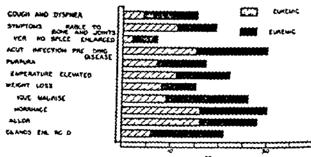
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LEUKEMIAS

Acute Lymphatic Leukemia in Childhood Dorothy Falkenstein and Willis M Fowler[5] (State Univ of Iowa) review 61 consecutive cases The children ranged in age from 3½ months to 15 years 0 5 years 26 6 10 years 20 and 11 15 years 15 Forty one were boys and 20 girls *This difference in sex incidence was more pronounced in the younger patients* the three patients above 13 were girls Total leukocyte counts on admission ranged from 1 900 to 1 000 000 per cu mm Thirty two patients had more than and 27 less than 12 000 leukocytes per cu mm at the time of admission Average percentage of lymphocytes in the leukemic group was 89 as compared with 85 in the aleukemic group In patients with extremely elevated leukocyte counts the immature lymphocytes predominated whereas immature cells were less frequent in the aleukemic phase With careful searching however examples of immature lymphocytes will be found in all cases Not all of these immature cells were typical large lymphoblasts many being small and but little larger than the mature lymphocyte The evidences of immaturity in these cells consisted of an evenly distributed threadlike or cordlike arrangement

(5) Am J Dis Child 65 445-454 M b 1943

of the chromatin of the nucleus giving it a light staining bland appearance the presence of nucleoli, a somewhat irregularly shaped nucleus and rather abundant cytoplasm With a low leukocyte count and a prepond



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erance of these relatively small lymphocytes the blood smear of a patient with this form of the disease may be easily confused with that of a person with aplastic anemia

With respect to onset course and symptoms of the disease there are no essential differences between pa

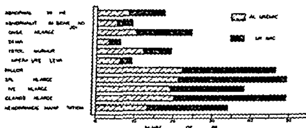


Fig 53 —Phy ical find ngs at time of h spitalizat on

tients with an elevated leukocyte count and those with a normal or low count Figure 52 shows the various complaints on admission and Figure 53 the findings on examination, both being separated into leukemic and aleukemic groups

Pains referable to the bones or joints were noted in 19 cases being somewhat more frequent in the aleukemic group When the clinical and hematologic features are otherwise typical of leukemia such a picture offers little diagnostic difficulty, but when articular manifestations occur early in a patient with an aleukemic phase of the disease the condition may be easily mistaken for rheumatic fever particularly if the pulse is rapid and a hemic murmur present At other times the disease is mistaken for infectious arthritis especially if the joints are red and swollen and fever is present

Roentgen therapy in acute lymphatic leukemia is effective in alleviating pressure symptoms due to enlarged glands but is of no value or is actually harmful in the absence of these symptoms Transfusions are of but slight palliative benefit

Myeloid Hyperplasia and Metaplasia Induced by Extracts of Urine from Patients with Myelogenous Leukemia Robert W Heinle Joseph T Wearn David R Weir and Frederick A Rose[6] (Western Reserve Univ) report that of 64 guinea pigs given extracts of urine from patients with chronic myeloid leukemia 31 (48 5 per cent) showed definite myeloid hyperplasia and metaplasia 29 showed no change and 4 showed an erythroblastic response Of 104 animals given urine extracts from individuals not having chronic myeloid leukemia only 16 (15 4 per cent) showed evidence of myeloid reaction Three of these had strongly positive myeloid reactions and included animals which had received respectively urine extract from a normal individual a patient with infectious mononucleosis and a patient with aplastic anemia Urine from patients with lymphoid leukemia gave weakly positive or negative results like those of normal persons The authors suggest that these false positive reactions may be due to some as yet unidentified substance which is present in all urine but is present in larger amounts in urine of patients with chronic myeloid

(6) Ann I t M d 17 902 919 D mber 1942

of the chromatin of the nucleus giving it a light staining bland appearance the presence of nucleoli a somewhat irregularly shaped nucleus and rather abundant cytoplasm With a low leukocyte count and a prepond

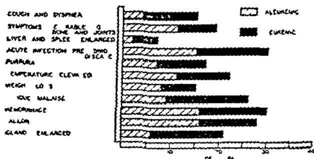


Fig 52 —Complaints at time of hospitalization

erance of these relatively small lymphocytes the blood smear of a patient with this form of the disease may be easily confused with that of a person with aplastic anemia

With respect to onset course and symptoms of the disease there are no essential differences between pa

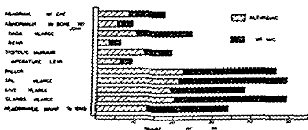


Fig 53 —Physical findings at time of hospital ation

tients with an elevated leukocyte count and those with a normal or low count Figure 52 shows the various complaints on admission and Figure 53 the findings on examination both being separated into leukemic and aleukemic groups

verted into an aqueous solution of dibasic sodium phosphate orally or parenterally Single oral doses varied from 1 to 20 mc and single intravenous doses from 0 2 to 2 mc Less than 3 Gm sodium phosphate was administered in each dose orally less than 1 Gm intravenously Frequency of administration followed no set rule some received the drug once weekly others three or more times a week Repeated small doses are usually preferable to the single large one Total number of doses varied according to the hematologic and clinical status and response of the patient No severe immediate reactions to the solution were observed

Four of eight patients with polycythemia vera were markedly improved both clinically and hematologically one was unimproved one only slightly improved and two have just begun treatment Remissions have lasted as long as six months and may last longer Two patients have begun to show hematologic relapse after six and seven months respectively Improvement may begin within two weeks of treatment but maximal effect is rarely obtained until treatment has been carried out for two or three months

One of five patients with chronic myelogenous leukemia obtained an excellent remission lasting several months A second patient under treatment seems to be responding satisfactorily Three patients in late stages were unimproved one dying before enough drug could be given and another becoming radiation fast because of previous roentgen therapy

Two of four patients with chronic lymphatic leukemia obtained good remissions duration of improvement cannot yet be gaged but one has remained in excellent condition for almost a year A third died of other causes soon after receiving the drug orally and a fourth only recently began treatment

None of the four patients with acute lymphatic leukemia was benefited One of the five patients with Hodgkin s disease who was becoming roentgen fast after two

leukemia Whether it is a *normal metabolic product present in excess in the urine of patients with chronic myeloid leukemia or an abnormal product not normally present in urine is not known* If it is an excess of a normal substance such excess might be due to overproduction of the substance or to decreased production of some neutralizing substance

Renal Complications of Leukemia Dudley Merrill and Henry Jackson Jr[7] (Harvard Univ) *direct attention to the frequency of renal failure in leukemia* The causes of this complication are nephrolithiasis infiltrative leukemic lesions of the kidneys obstruction of the renal blood vessels or ureters by leukemic tissue or finally nonleukemic degenerative lesions of the kidneys The rare occurrence of gout in cases of leukemia is noted. Three cases exemplifying these complications are reported

Case 1 —Man 61 had chronic myeloid leukemia and gout. During his last four years of life practically all his symptoms were due to gout although renal insufficiency was a factor in the last 18 months At autopsy the diagnosis of leukemia was confirmed and multiple renal calculi (pelvic and ureteral) were found that doubtless were the contributory, *if not the main cause of the impaired renal function*

Case 2 —Woman 28 had acute lymphatic leukemia She experienced an episode simulating acute nephritis with edema hypertension convulsions and nitrogen retention, which subsided following x ray therapy to the kidneys At autopsy she was found to have multiple renal calculi and both ureters and renal arteries and veins were embedded in tumor tissue that was diagnosed as Hodgkin s sarcoma

Case 3 —Woman 68 had leukemia *thrombophlebitis of both iliac and femoral veins and multiple small pulmonary infarcts* Death occurred from uremia *Her renal insufficiency* was due partly to circulatory failure and anemia and partly to blocking of the glomerular capillaries with leukemic cells

Clinical Experience with Radiophosphorus in Treatment of Certain Blood Dyscrasias Thomas Fitz Hugh Jr and Philip J Hodes[8] (Univ of Pennsylvania) report results in 38 patients given radiophosphorus con

(7) New England J Med 8 71 276 Ma 4 1943
(8) Am J M Sc 204 66 -665 November 194

Spontaneous and Hereditary Thrombopenic Purpura in Mother and Two Sons L Holland Whitney and A Sidney Barritt Jr[9] (Brooklyn) present evidence sup porting the concept of congenital thrombopenia

Woman had splenectomy for thrombopenic purpura at 14 After splenectomy, she remained well except for an occasional purpuric spot When 26 she became pregnant antepartum period delivery and postpartum period were uneventful The infant weighed 6 lb 4½ oz and was covered with many purpuric spots at birth Platelet count was 80 000 bleeding time 1 minute and clotting time 3½ minutes On the third day the baby showed signs of intracranial hemorrhage and died in 24 hours Ten months after delivery the mother be came pregnant again Laboratory studies during early preg nancy showed 62 000 platelets no retraction of clot in 33 hours and prothrombin time 28 per cent faster than normal Vitamins calcium synthetic vitamin K (menadione) and liver extracts were given Labor was normal and postpartum course again uneventful The infant weighed 5 lb 5½ oz The skin was clear at birth but petechial patches soon appeared in the groins and on the ankles Platelet count was 90 000 bleeding time 11 minutes and clotting time 1½ minute Prothrombin time was 28 per cent of normal Transfusion of whole blood and administration of synthetic vitamin K ascorbic acid and koagamen failed to prevent spreading of hemorrhagic spots and the baby died 24 hours after birth

Diagnosis of hemorrhagic disease of new born was not tenable The spontaneous and immediate appearance of hemorrhagic phenomena in both infants following birth was not characteristic of hypoprothrombinemia Pro thrombin studies made on the second baby were not unusual for infants in this age group Vitamin K wa given the mother during pregnancy and to the baby soon after birth Definite platelet deficiency was present in both infants Neither child responded to whole blood

Advisability of pregnancy in a woman with essential thrombopenic purpura must be considered The patient

(9) Am J Dis Child 64 705 713 Oct h 1942

years of treatment was considerably improved for a few months following use of the drug The others were not benefited, one of them having a huge mediastinal mass that did not respond to P^{32} but did regress with roentgen therapy Two of six patients with lymphosarcoma had good remissions two were benefited for several months but both suffered relapses One patient with multiple myeloma was not benefited One patient with reticulo endotheliosis who had not reacted to roentgen therapy improved remarkably with radiophosphorus therapy One patient with reticulum cell sarcoma had become roentgen fast and was not benefited by moderate doses of radiophosphorus Metastatic carcinoma in three patients, two with extensive gallbladder carcinoma and one with disseminated breast malignancy, was not benefited The total amount of drug given was probably not enough to affect such radio resistant neoplasms

The authors conclude that radiophosphorus is at least equal in value to older methods of radiation therapy in certain malignant blood dyscrasias and that it may produce more prolonged remission in chronic leukemia and polycythemia vera. At present the supply is inadequate and the newly discovered metallurgic uses of the cyclotron and its products are threatening to eliminate its use for clinical medicine altogether for the duration of the war

and she was discharged on the ninth day Ten days later she was readmitted with profuse vaginal bleeding of 12 to 18 hours duration Blood studies showed erythrocytes 3 880 000 leukocytes 11 200 hemoglobin 65 per cent platelets 25 000 Bleeding time was 10 minutes and coagulation time 3½ minutes with a nonretractile clot Direct blood transfusions and uterine packing failed to control the vaginal bleeding Hemoglobin and platelet levels continued to drop and the spleen about twice normal size and two splenuli were re moved Histologic diagnosis was hyperplastic spleen on the basis of thrombopenic purpura

Uterine bleeding ceased almost immediately Two days later the platelet count rose to 268 000 and mounted steadily to 826 000 on the thirteenth day after which there was a gradual decline to 124 000 on discharge 25 days after operation Two years later the platelet count was 75 000 and five years later 100 000

Two years and six months after splenectomy the patient gave birth to a full term living female child weighing 7 lb 13 oz, with a normal ante and postpartum course and no signs or symptoms of purpura Twenty four hours after de livery the infant had petechial purpura which disappeared in a few days Examination of the infant s blood revealed anemia prolonged bleeding time and decided decrease in the platelet count Examination at 28 months showed 3 850 000 erythrocytes 8 200 leukocytes 79 per cent hemoglobin 1½ minute bleeding time and 3 minutes coagulation time

Four and six years after splenectomy the patient again gave birth to living male children making a total of three living children after operation the last two apparently free from any blood dyscrasia In the last two pregnancies the mother had a normal antepartum course free from any pur pura but immediately after the placenta was delivered in each instance she had a sudden attack simulating pulmonary em bolism from which she soon recovered These attacks may have been related to her history of thrombopenic purpura.

Thrombocytopenic Purpura Caused by Sulfonamides

Purpura haemorrhagica must now be recognized as a possible serious though infrequent complication of sul fonamide therapy Eight cases have been reported (see table) These include three reported herein by I Whittington Gorham Simon Propp Joseph L Schwind and David R Climenko[2] (Albany Med College) There

(2) Am. J M S 05 246 57 F b u ry 1943

in the present case has been advised against further child bearing and has remained clinically well

[Note that despite previous splenectomy this mother had a low platelet count and both children died from this cause. The next article describes the more successful result of splenectomy in permitting delivery of infants who survived. Nevertheless, thrombopenic purpura in pregnancy is not always an indication for splenectomy termination of pregnancy or probable infant death.—Eds]

Thrombopenic Purpura Complicating Pregnancy Treatment of a patient by splenectomy resulting in clinical cure and followed by three full term pregnancies is reported by Adrian X Urbanski and Cyril I Hutner[1] (Perth Amboy N J)

Woman, 32 who has been followed for 18 years exhibited hemorrhagic diathesis since the age of 14 Manifestations included prolonged bleeding following small cuts numerous attacks of epistaxis severe hemorrhage after exodontia and menorrhagia At 16, she was hospitalized for 10 days for severe epistaxis At 21 she was again admitted, complaining *of metrorrhagia for 12 days She was almost exsanguinated,* with considerable air hunger Blood studies revealed 1,580 000 erythrocytes 11 per cent hemoglobin (Sahli) and 5 400 leukocytes Her condition was controlled with blood transfusions and a gradual rise in erythrocyte hemoglobin and platelet levels followed This period of hospitalization was marked by profuse epistaxis which required repeated nasal packing for control She left the hospital after five weeks with erythrocyte count 3 410 000 and hemoglobin 50 per cent Two years later she had a miscarriage with some hemorrhage that was controlled by uterine packing

In 1935, at 25 she was again hospitalized at full term with breech presentation She had slight edema of the fingers and arms slight gingival bleeding and petechiae and ecchymoses in the skin Blood studies revealed 5 590 000 erythrocytes, 19 400 leukocytes 95 per cent hemoglobin and 50 000 platelets Wassermann reaction was negative coagulation time was 3½ minutes bleeding time 8 minutes The tourniquet test was positive During the second stage of labor a stillborn fetus was rapidly delivered, which presented generalized petechial hemorrhages of the skin, a large scrotal hemorrhage and hemorrhages in the brain pleuras thymus kidneys, testes and heart

Purpura in the mother diminished six days post partum

(1) J A M A 120 754 756 Nov 7 1942

were four deaths Fatal purpura has been caused by sulfanilamide sulfapyridine and sulfadiazine In the one reported case of purpura following use of sulfathiazole recovery occurred

In at least two and possibly three of the four fatal cases the drug was continued for 24 to 48 hours after petechial hemorrhages or bleeding had occurred In the four cases of recovery the drug was stopped on *first appearance of hemorrhagic manifestations* This is important Since thrombocytopenia precedes the purpura it is obvious that detection of reduction of blood platelets in the blood smear would be of *greater value as a danger signal than the finding of* a few petechiae or slight hemorrhage

The bone marrow shows no significant change in these cases The amount of drug necessary to produce purpura is extremely variable, death occurred with as little as 7 Gm In one case purpura appeared after administration of 5 5 Gm sulfathiazole but after recovery 15 Gm more was given without untoward effect

No definite statement can be made to explain the blood dyscrasias which occur in certain individuals following sulfonamide therapy The similarity in chemical structure however between the sulfonamides and such known hematotoxic agents as benzol and aniline makes the similarity in the clinical manifestations of their toxic reactions all the more striking When it is realized that the organism handles these two types of substances in a fundamentally similar manner that they are chemically closely related and *that they are capable of producing identical pathologic* lesions in the bone marrow it is reasonable to assume that the production of blood dyscrasias by the two types of substances involves the same fundamental mechanism (Fig 54)

The structural relationship between benzol aniline and the sulfonamides is clearly shown by the structural formulas (Fig 54) In the case of the three sulfon

RECORDED CASES OF THROMBOCYTOPENIC PURPURA DUE TO SULFONAMIDES

Author	Age and Sex	Disease Treated	Drug	Total Dosage No of Days	Hgb %	R B C (Millions)	W B C (Thousands)	Platelet Count (Thousands)	Comment
Markel and Rike 1930	59, M	Cystitis	Sulfanilamide	7 Gm, 4 da	50	2 2		180	Died 7th day
Russell and Page 1940	41 M	Pul tb pneumonia	Sulfapyridine	45 Gm 10 da	56	3 4	5 0	34	Recovered
Russell and Page 1940	60 M	Pneumonia	Sulfapyridine	3 Gm 7 da	11	0 98	19 0	None in smear	Died 14th day, 1 basophil
Goldbloom Greenwald and Reinstein 1941	?0 F	Pneumonia	Sulfapyridine	32 Gm 8 da	44	2 8	33 0	25	Recovered myelocytes 12%, metamyelocytes 15% leukemoid reaction
Rosenfeld and Feldman 1942	37 M	Ureteral calculus pyelonephritis	Sulfathiazole	5 5 Gm 3 da	50	2 6	12 4	2	Recovered 15 Gm sulfathiazole given later without untoward effect
Gorham Propp Schwind and Climenko, 1942	23 M	Coryza laryngitis	Neoprontosil sulfanilamide	4 Gm, 2 da. 3 Gm 1 da	85	4 6	8 1	36	Recovered 1 myelocyte
Gorham Propp Schwind and Climenko, 1942	62 M	Pneumonia	Sulfapyridine	18 Gm 3 da 30 Gm 5 da.	49	3 3	11 8	Very scarce	Died 12th day
Gorham Propp Schwind and Climenko 1942	60, F	Fracture operation infection	Sulfadiazine	25 Gm, 6 da.		3 1	15 0	None in smear	Died 8th day

The multiplicity of the clinical manifestations of blood dyscrasias resulting from administration of the sulfonamides is duplicated by benzol and aniline intoxication The effect may be on the cells of the peripheral circulation or on any or all of the series of blood cells produced in the bone marrow Thus following administration of sulfonamides as well as in benzol or aniline intoxication there may occur granulocytopenia hemolytic anemia leukemoid reaction thrombocytopenic purpura and possibly aplastic anemia

Rare Type of Acute Thrombocytopenic Purpura Widespread Formation of Platelet Thrombi in Capillaries Mark D Altschule[3] (Harvard Univ) reports a case resembling five cases previously reported in the literature all in females and fatal after a short illness In 1936 Baehr Klemperer and Schifrin reviewed four cases with common clinical and pathologic findings and noted a resemblance to one of Moschcowitz They suggested that the profound thrombocytopenia might be due to withdrawal of enormous numbers of platelets from the circulation and that the phenomenon might be present in other cases of thrombocytopenic purpura

Woman 50 was hospitalized after four days illness with malaise and abdominal pain with severe headache dizziness and vomiting of bright red blood Examination revealed petechiae on legs and face slight smoothness of edges of the tongue tender abdomen enlarged liver and palpable spleen Urine contained some albumin erythrocytes and leukocytes but no Bence Jones protein specific gravity was 1 002 1 012 Blood studies showed 1 800 000 red cells hemoglobin 33 per cent 13 400 white cells with 80 per cent polymorphonuclears 15 per cent lymphocytes 4 per cent monocytes and 1 per cent eosinophils 54 000 platelets 2 2 per cent reticulocytes bleeding time over 30 minutes and clotting time 2 minutes with clot retracting poorly Nonprotein nitrogen level was 33 mg cholesterol 313 mg per 100 cc with 142 mg per 100 cc esters uric acid 5 6 mg serum protein 6.1 Gm icteric index 10 There was no free hydrochloric acid in a fasting gastric specimen Bone marrow biopsy and lumbar puncture revealed normal findings

(3) N w E gla d J M d 227 471-479 Sept 24 194_

amides *sulfapyridine sulfathiazole and sulfadiazine* the R in the formula represents a heterocyclic ring

In the body analine is converted to phenylhydroxyl amine and then to p aminophenol This oxidation compound is excreted in combination with sulfate as an ethereal sulfate A definite increase in ethereal sulfate output is characteristic of benzol and aniline poisonings and one of the first clinical manifestations of intoxication with such substances is the lowering of the ratio of excreted inorganic sulfur to total sulfur

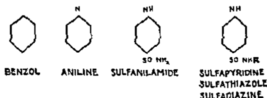


Fig 54 —Structural formulas of sulfonamides

in the urine James has been able to isolate a series of oxidation products of sulfanilamide which are analogous to the known oxidation products of aniline from the urines of patients receiving therapeutic doses of the drug He suggested that some of the toxic effects noted by clinicians might be due to these oxidation products and pointed out that both the p aminophenol and the hydroxylamine compounds, in their unconjugated form are capable of producing degenerative blood changes

In addition to possessing a potential toxic action on the hemopoietic mechanism all of these compounds (benzol aniline and the sulfonamides) have a direct effect on the cells of the peripheral circulation None are hemolytic substances but all will accelerate the rate at which *hemolysis occurs in the presence of a* known lysin This property may account for the hemolytic anemias sometimes occurring during sulfonamide therapy

plasma free from active calcium ion is treated with chloroform a fraction of plasma globulin appears changed or modified so that it exhibits property of an enzyme This preparation which appears to destroy fibrinogen and to lyze fibrin contains neither pro thrombin nor fibrinogen

When the smallest quantity of the preparation which completely lyzed fibrinogen and failed to clot fibrino gen solutions was added to 0 1 ml plasma under standard conditions clot always occurred Much higher concentrations could be added before clot formation was prevented This indicates marked inhibition of lytic effect of the preparation by plasma Observed re sults indicate that prothrombin might be the inhibitor

The inactive progenitor of the fibrinolytic factor in plasma is uncertain However the impure protein frac tion contained in globulin substance which has no proteolytic activity can be activated by chloroform The proteolytic activity of such preparation is the same as that obtained from whole plasma Similarly plasma euglobulin equally inactive as a proteolytic enzyme can be activated by chloroform to develop marked fibrinolytic action although supernatant liquid from the euglobulin preparation is not a source of sig nificant amounts of enzyme

There is no indication of general species specificity Proteolytic activity is present in chloroform plasma globulin preparations of human dog beef rabbit and swine blood Horse blood is an exception in that prepara tions of such blood are only minimally potent

In many respects the chloroform plasma preparation resembles trypsin in its action on plasma fibrinogen and prothrombin Its role in blood coagulation is not clear Undoubtedly the preparation can cause coagula tion of oxalated blood and fibrinogen solution with subsequent lysis

Intravenous Use of Vitamin K_1 Oxide is reported by William A Davis Howard A Frank Alfred Hurwitz

She was given high vitamin and protein diet with additional vitamins Rectal temperature rose from 98 6 101 to 107 F on the ninth day She was given 500 cc citrated blood the third fifth and eighth days and 1,000 cc blood the seventh day, and physiologic saline and glucose Red cell count generally remained between 1,600,000 and 1 900,000 White cell count varied from 10,000 to 21 000 with decrease in polymorphonuclears to 52 to 58 per cent the seventh day Platelet count decreased to 11 000 and reticulocytes varied from 7 to 12 per cent Many stippled and a few nucleated erythrocytes were seen The third day mental confusion and fresh purpuric spots appeared The sixth day, with disorientation and elevation of temperature, icteric index was 18 Roentgen signs of pneumonia led to sulfathiazole therapy, but she died after vomiting several hundred cubic centimeters of coffee-ground material

Autopsy revealed hemorrhages into viscera with widespread petechiae Numerous capillary thrombi were found in pancreas and heart, moderate number in adrenals kidneys and gastro intestinal tract and a few in spleen and liver Thrombi in a few glomerular capillaries also involved the afferent arterioles The thrombi varied from a few platelets adherent to endothelium to masses of platelets The capillary endothelium showed proliferation in these areas, growing over the masses of platelets sometimes remaining thickened after resorption of most of the thrombus Despite widespread thrombosis, there was little evidence of parenchymal necrosis

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HEMOPHILIA AND OTHER VARIETIES OF DEFECTIVE BLOOD COAGULATION

Studies on Blood Coagulation Proteolytic Enzyme Prepared from Calcium and Platelet-Free Normal Human Blood Plasma According to Henry J Tagnon Charles S Davidson and F H L Taylor[4] (Harvard Univ), the concept that blood plasma may contain a proteolytic enzyme system associated with blood coagulation is not new Evidence from investigations in unrelated fields points to existence of such a system but precise experimental evidence is lacking

The authors give a method for preparing an active enzyme from blood plasma When platelet free human

(4) J Clin In estig tion 21 5 531 S pt mber 1942

ers admitted to the obstetric ward representing the low est income group of a metropolitan area It was assumed that dietary deficiencies and obstetric complications would be maximal in this group and that if these fac tors contribute materially to occurrence of hemorrhage in new born any procedure directed toward reduction of neonatal hemorrhage should manifest its greatest benefits in these patients

A single dose of 5 mg vitamin K was given orally on admission to the mothers of 1 151 infants the in fants of 1 594 mothers who received no vitamin K served as controls There was no appreciable ill effect of the vitamin on the mothers While the vitamin was effective in raising the blood prothrombin levels of both the mothers and infants it had no evident effect in reducing incidence of neonatal hemorrhage If an elevated blood prothrombin level is a significant factor in preventing such hemorrhage the results of this sur vey remain abstruse

[This report deserves careful study in the original It is of course possible that the violence of birth is such as to cause too gross lesions of the blood vessels for the effect of better blood clotting due to vitamin K to be statistically perceptible in a series in which the incidence of hemorrhage is only 1 4 1 7 per cent

The following three articles are concerned with the use of dicou marin as a means of prolonging the coagulation time of the blood especially in order to prevent postoperative thrombosis An in herent difficulty with the method is the inability of synthetic vitamin K to shorten the coagulation time if bleeding begins However very recent reports suggest that large doses of vitamin K oxide may be so effective —Eds]

A Preparation from Spoiled Sweet Clover Edgar V Allen Nelson W Barker and John M Waugh[8] (Mayo Clinic) present a clinical study of 3 3 methylene bis (4 hydroxycoumarin) which prolongs coagulation and prothrombin time of the blood The effect of dicoumarin seems to be on prothrombin only inhibiting its action by destroying it or by interfering with its production Secondary effects are interference with normal clot retraction and increased sedimentation rate If enough

(8) J A M A 120 1009 1015 N 8 194

and Arnold M Seligman[6] (Peter Bent Brigham Hosp) After the synthesis of vitamin K_1 Fieser postulated that this light sensitive vitamin probably did not exist as the quinone in the green alfalfa leaf from which it had been isolated He suggested that vitamin K_1 may be present in the green leaf as its oxide Tishler, Fieser and Wendler synthesized the oxide and found it to be readily reducible to the hydroquinone of vitamin K_1 Fieser Tishler and Sampson found the oxide to be three times as stable as the quinone on exposure to ultraviolet light and hardly distinguishable' from the vitamin itself in assays on chicks These workers were impressed with a similarity in properties between the synthetic oxide and a colorless fraction isolated from alfalfa by Fernholz Ansbacher and co workers

Because of the ease of preparation of the oxide from vitamin K_1 and its stability to ultraviolet rays, it was felt that the substance merited clinical trial Although the oxide like the vitamin itself is not soluble in water it was found that a stable suspension of therapeutic doses suitable for intravenous injection could be made in volumes as low as 10 cc This seemed to increase the likelihood that the oxide would be a more generally useful agent for intravenous therapy with vitamin K

Vitamin K_1 oxide was used intravenously in two patients The first of these a patient with acute hepatitis and obstructive biliary cirrhosis received 6 mg the second who had obstructive jaundice from metastatic carcinoma was given 10 mg In both the single intravenous dose of vitamin K_1 oxide produced in the low prothrombin values the rapid response and prolonged action noted with the vitamin K_1

Does Antenatal Use of Vitamin K Prevent Hemorrhage in the New Born Infant? John Parks and Lewis K. Sweet[7] (Washington D C), made a clinical analysis of gross hemorrhage occurring in the infants of moth

(6) Arch Surg 46 296 300 F bruary 1943
(7) Am J Obst & Gynec. 44 432-44 September 194

given and this is repeated until bleeding stops Although the prothrombin time may again be greatly increased after a temporary decrease bleeding stopped as result of transfusion seldom recurs

Because of the latent period between administration and impairment of prothrombin time dicoumarin can not be used when a quick anticoagulant effect is desired Under these circumstances heparin is given intravenously and dicoumarin orally at the same time Since heparin does not influence prothrombin time the effect of dicoumarin can be ascertained by determining prothrombin time even when heparin is given simultaneously When the effect of dicoumarin is adequate heparin is discontinued Heparin is best given by continuous intravenous administration but may be given by the method of Crafoord and Jorpes who inject 50 100 mg directly into a vein every six hours Such injections usually need to be continued 36-48 hours

Dicoumarin should not be used for patients who are bleeding Its use is particularly dangerous in subacute bacterial endocarditis Its effect on prothrombin time is excessive in patients with renal insufficiency or inadequate urinary excretion The authors have administered dicoumarin in 374 cases in an effort to prevent arterial or venous thrombosis and pulmonary embolism or to prevent extension of intravascular thrombosis In postoperative pulmonary embolism infarction and postoperative thrombophlebitis the drug was administered as soon as clinical diagnosis was made In a few cases heparin was used until dicoumarin became effective When thrombophlebitis or pulmonary embolism had complicated a previous operation and when abdominal hysterectomy or other operation was performed on a patient who had not had thrombophlebitis or embolism dicoumarin administration was begun approximately 24 hours after operation Pulmonary infarction developed in one patient with prothrombin time of 26 seconds and thrombophlebitis in two with

dicoumarin is given, coagulation time is prolonged and bleeding may occur In this connection (except in sub acute bacterial endocarditis), the danger of bleeding is minimal unless the prothrombin time is greatly prolonged Hence it should not be given unless the prothrombin time can be determined daily

The authors administer dicoumarin orally There is a lag or latent period of 24 to 48 hours before appearance of the effect Single doses of 200 or 300 mg dicoumarin are given the first day and 200 mg the second day Subsequent daily dosage is based on the prothrombin time of the blood drawn that day keeping the latter between 35 and 60 seconds If on the morning of the third day the prothrombin time exceeds 35 seconds dicoumarin is withheld if it is less than 35 seconds 200 mg is administered in a single dose On each subsequent day a similar plan is followed, continuing administration as long as the effect of dicoumarin is desired When dicoumarin is discontinued prothrombin time remains elevated for three to seven days then gradually returns to normal The response varies in different patients In some instances administration of 200 to 300 mg on two successive days causes satisfactory elevation of the prothrombin time for several days In others the amount must be given one to three more days before a satisfactory effect is produced

As a prophylaxis against thrombosis in postoperative patients dicoumarin was given the day following operation and long enough to assure elevation of prothrombin time until the patient was active A satisfactory effect is desired for about 10 days after pulmonary embolism and after the onset of acute thrombophlebitis The effect of dicoumarin must be controlled in case bleeding occurs Synthetic vitamin K is largely ineffective The authors give a transfusion whenever alarming hemorrhage occurs as happens infrequently If bleeding is not controlled another transfusion is

crease in capillary fragility was detected even in hemorrhagic cases Incidence of hypochlorhydria or achlorhydria was not significantly greater in the hemorrhagic group Toxicity on the basis of retention due to renal dysfunction could not be established in patients presenting hemorrhages although urea nitrogen nonprotein nitrogen urea clearance and urinary studies were conducted Most of the patients were treated during the hot summer months and Link had observed that an abnormally high environmental temperature might enhance the action of dicoumarin in animals Definite conclusions cannot be made regarding this factor

The question whether liver damage acts as the mechanism by which prothrombin is inactivated is not definitely decided The time required for restoration of normal prothrombin levels and the duration and intensity of hemorrhagic complications did not differ significantly in patients who received vitamin K substitutes and in those who did not

The therapeutic value of dicoumarin has not yet been clearly established The majority of 40 patients received 300 mg after breakfast daily the first two or three days Subsequent doses were administered at two to three day intervals depending on the degree of prothrombin time prolongation obtained with 25 per cent diluted plasma The levels between which the authors have attempted to maintain prothrombin times are 30 35 seconds for undiluted plasma and 70 90 seconds for 25 per cent diluted plasma Hence when prothrombin time falls below 30/70 a dose is indicated If however the prothrombin time exceeds 35/90 dicoumarin is withheld

A Critical Study of the Action of Dicoumarin is presented by Charles S Davidson and Harriet MacDonald[1] (Harvard Univ) Eight persons aged 12 69 were studied Two were convalescent from mild illnesses and may be regarded as normal four had thrombophle

(1) Am J M S 205 24 33 J u ry 1943

prothrombin times of 35 and 45 *seconds* These three are the only instances of clinical thrombosis in the 374 cases during the period of prothrombin time elevation Except in two cases, moderate or severe bleeding occurred only when prothrombin time was above 60 seconds

Dicoumarin 3 3 Methylene Bis (4 Hydroxycoumarin) Irving S Wright and Andrew Prandoni[9] (Columbia Univ) report cases *illustrating the hemorrhagic phenomenon following dicoumarin administration* A single large dose of 600 mg produced less physiologic and definitely less *toxic effects than* total equivalent doses administered in portions of 100 mg daily a phenomenon Link and his associates *previously* noted in animals and attributed *to imperfect* intestinal absorption The earliest toxic signs most frequently noted were lassitude and general malaise with aching in the costovertebral angles By using smaller doses the authors are practically able to eliminate the risk of hemorrhage

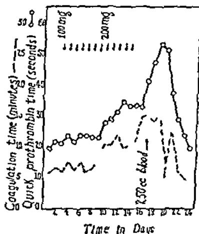


Fig 55 —Patient, 37 135 lb with diagnosis of thrombo ngiit obl te ns response of coagulation and prothrombin times to administration of dicoumarin.

Various factors were examined to determine a possible cause for the variable response of patients to dicoumarin administration Analysis of clinical and laboratory data revealed the following facts Incidence of toxic reactions was not significantly influenced by age or sex *No significant correlation* existed between malnutrition and frequency of toxic reactions No in

(9) J A M A, 1 0 1015 10?1 Nov 28 1942

trations of normal plasma mixed with the same plasma passed through a Seitz filter five times Plasma so filtered becomes incoagulable with thromboplastin and calcium for more than two hours With this curve a prothrombin time of about 60 seconds corresponded to approximately 10 per cent 90 seconds to 5 per cent and 150 seconds to 2 5 per cent of the normal plasma prothrombin concentrations respectively A prothrombin time of greater than 150 seconds was simply called less than 2 5 per cent of normal In many of the patients given dicoumarin the Quick prothrombin time was extraordinarily prolonged Yet it was found that when the prothrombin times on one occasion were over 1 hour and on another 40 minutes not only did the whole blood still clot but it did so in the relatively short time of 17½ and 19 minutes respectively

The effect of dicoumarin on the coagulation time of blood measured in glass and lusteroid tubes was extremely variable In general coagulation time became prolonged as the prothrombin concentration reached low levels However there was no parallelism of the two in any one patient and further some of the patients had a moderately prolonged coagulation time without profound lowering of the prothrombin concentration The coagulation time measured in lusteroid tubes showed a much greater prolongation with reduction in prothrombin concentration than that measured in glass tubes Furthermore the rise in clotting time in lusteroid tubes was sometimes but not always 24 hours earlier than the change detected in the clotting time in glass Occasionally the blood in lusteroid tubes failed to clot under 24 hours

Because of its chemical constitution and because prothrombin is generally accepted as being manufactured in the liver hepatic function tests were done on the individuals receiving dicoumarin No significant change was found

bitis one had endocarditis lenta and the eighth patient had survived suture of a wound in the heart

The first action of dicoumarin was always manifest as a fall in prothrombin concentration Three of the patients responded within 24 hours, whereas the rest required 2 5 days for a fall to 30 per cent of normal prothrombin concentration Several factors appear to modify the unpredictable time of onset of the action the size of the initial dose and of subsequent doses in relation to body weight the initial level of prothrombin concentration in the blood and variable individual response The effect of dicoumarin once low prothrombin concentrations are reached is quite prolonged In one apparently normal individual who received a single dose of 15 mg per Kg body weight a prothrombin concentration of below 30 per cent of normal was maintained for five days and the concentration did not return to normal limits for five more days Most patients received an initial dose of 3 to 12 mg per Kg body weight and thereafter a daily dose of 0 1 to 0 2 Gm With this dosage the prothrombin concentration was maintained at extremely low levels, and with one exception, 5 11 days were required after administration of the drug was stopped before the concentration rose above 50 per cent When this level was reached return to normal was always prompt

The prothrombin time with the thromboplastin used has a normal value of 25 to 30 seconds The amount of prolongation of the Quick prothrombin time is of interest when interpreted as prothrombin concentration and especially when this concentration is *compared* with the plasma recalcification time and coagulation time of whole blood In calculating prothrombin concentrations a curve was used which was obtained by plotting the prothrombin time of a series of appropriately modified plasmas To accomplish this the prothrombin time was determined from varying concen

DISEASES OF THE KIDNEY

Renal Pathologic Changes in Hypertension and Glo merulonephritis To interpret pathologic changes char acteristic of these diseases in terms of the inevitable effects of these structural alterations on the general functional capacity of the kidneys J P Simonds (Northwestern Univ) considers it important to have clear concepts of (1) the normal structural pattern of the kidneys (2) the mechanism by which the kidneys perform their functions through the medium of their structural pattern and (3) the basic changes induced in their structural pattern by disease

Each human kidney contains about a million anatomic and physiologic units or nephrons and each nephron consists of a glomerulus and a tubule The glomerulus is a tuft of nonanastomosing capillaries lined with epithelium and covered with a layer of thin epithelial cells This mass which forms a biologic filter is invaginated into the upper end of the tubular por tion of the nephron Each tubule is divided into four portions The proximal convoluted tubule conserves by selective reabsorption from the glomerular filtrate substances needed by the body This process requires the simultaneous obligate reabsorption of a volume of water proportional to the quantity of solute ab sorbed The distal convoluted tubule alters the reaction of the urine and renders it acid Intercalated between the proximal and the distal convoluted tubule is Hen le s loop a structure peculiar to the kidneys of birds and mammals the only animals capable of secreting a urine hypertonic to the blood The collecting tubule in which the distal convoluted tubule ends is a con duit without specific function except to conduct the finished urine to the renal pelvis

(3) J A M A. 120 89 93 Sept 1 194

Whole blood transfusion was found to have only a transitory effect or no effect on the abnormal clotting mechanism in patients receiving dicoumarin

The authors results agree with those of others that no effect on prothrombin concentration is produced when as much as 60 mg synthetic vitamin K was administered intramuscularly to patients receiving dicoumarin with a prothrombin concentration of less than 2 5 per cent of normal

The authors suggest that the variable effect of dicoumarin on blood coagulability, its prolonged action after discontinuation and its difficulty in control render it a poor heparin substitute and that great caution must be used in its administration

peritubular capillaries may be responsible for rapid diffusion of almost all glomerular filtrate through the layer of dead functionless tubular epithelium This explains the oliguria and anuria characteristic of mercury bichloride poisoning

Pathologic conditions resulting in renal insufficiency have in common interference with the blood supply to the glomerular and peritubular capillaries Even with severe renal disease kidney competence may be main tained by one or more of several possible adaptations When many glomeruli have been destroyed as in chronic glomerulonephritis increased blood flow through a smaller number of pervious glomeruli under increased hydrostatic pressure may maintain the total glomerular filtration at a normal level Two chief conditions threat ening kidney efficiency are (1) arteriolar sclerosis with narrowing of the lumen of the afferent arteries to the glomeruli and (2) primary disease of the glomeruli Pathologic changes leading to hypertension occur in three stages (1) functional vasoconstriction (2) hy pertrophy of the muscular coat and hyperplasia of the elastic lamina of the afferent arteries and (3) transfor mation of the arteriolar walls into hyaline tubes with narrowed lumens

It is thought that because the acute glomerulonephritis of scarlet fever is more exudative than other forms of the disease scarlatinal nephritis rarely becomes chronic or fatal In other types of glomerulonephritis the pri mary glomerular lesion is proliferative Progressive glomerular destruction finally exceeds the functional kidney reserve and retention of nitrogenous waste prod ucts begins With rapid progress uremia may suddenly occur With slow progress hypertension may proceed more rapidly than the diminution in total filtration sur face of the glomeruli so that some patients may die of congestive failure of a hypertrophied heart before the disease has progressed to the uremic stage

Changing Concepts of Pyelonephritis According to

Total blood flow through the kidney has been estimated at 500 1 100 cc per minute Pathologic changes which decrease blood flow *through the glomeruli* will decrea e glomerular filtration and also the blood supply to the tubules This is the chief factor in tubular atrophy in chronic glomerulonephritis and advanced hypertension The hydrostatic pressure of the blood in the glomerular capillaries is higher than in any other system of capillaries in the body and has been estimated at 60 per cent of the pressure in the aorta, or 72 mm Hg The pressure is maintained at a high level throughout the course of the glomerular capillaries because of the relatively small size of the efferent arteries through which the blood leaves the glomeruli The efferent arteries are short and quickly break up into a network of capillaries that surround the tubules from their own glomeruli of origin and anastomose to some extent with capillaries from other efferent arteries About 100 L of a watery solution of the crystalloid substances in the plasma in the same concentration as they existed in the plasma passes through *the glomerular filter each 24 hours* Waste of needed materials is prevented by selective absorption by the tubules The proximal convoluted tubules reabsorb from the glomerular filtrate all the sugar and varying *amounts of urea chlorides and other substances* according to body needs together with a sufficient amount of water to hold these substances in solution This portion of the nephron excretes diodrast and phenolsulfonphthalein but does *not normally excrete* the usual metabolic waste products Metallic poisons are not reabsorbed by the tubular epithelium but are concentrated in the tubular lumens by water absorption This portion of the nephron *is vulnerable to* metallic poisons and this is the mechanism by which the proximal convoluted tubules are damaged by dialyzable poisons which are not *selectively* reabsorbed The high osmotic pressure of *plasma proteins in the*

result of these changes is ischemia Furthermore there is the added possibility of arterial hypertension

The concept of a relationship between renal ischemia and hypertension is of primary importance Goldblatt found that presence of normal renal tissue prevents development of hypertension due to ischemia However clinical and pathologic evidence indicates that in man unilateral renal ischemia may result in hypertension Such patients are susceptible to surgical treatment In a few cases marked temporary and sometimes permanent relief of hypertension has followed removal of a unilateral pyelonephritic kidney

Pyelonephritis may be the starting point of hypertension although it is doubtful if it is as dominant as some consider it Renal ischemia may be the essential factor responsible for hypertension associated with pyelonephritis No satisfactory hypothesis has been suggested to explain the relation between ischemia and hypertension Formation of a pressor producing substance renin by the ischemic kidney may be accepted a concept strengthened by Houssay s recent experimental work Attention has been directed to the so called juxtaglomerular apparatus There is no proof that it is directly connected with regulation of blood pressure or with controlling blood flow through the kidneys but evidence is suggestive and worthy of careful study The significant frequency of relation between pyelonephritis and the mechanism of hypertension demands further study

Lipid Nephrosis The term lipid nephrosis was first used by Muller to distinguish the purely degenerative type of renal lesion from the inflammatory type It has since come to designate a malady characterized by insidious onset generalized recurrent edema normal blood pressure massive albuminuria normal blood urea content high serum lipid level and low value for total serum protein and for albumin Epstein suggested that the cause of lipid nephrosis is extrarenal and that the

William Boyd[3] (Univ of Toronto), a gradual change has taken place in the concept of pyelonephritis including two new ideas of fundamental importance First is the concept of an atrophic contracted kidney with insufficiency as an occasional end result second is realization of possible relation to arterial hypertension

The chief causative organisms of pyelonephritis are streptococci, staphylococci and Bacillus coli which may reach the kidney by blood stream or lower urinary tract. Urinary tract obstruction may favor hematogenic or ascending infection

Pyelonephritis is fundamentally an inflammation of the interstitial tissue which may be acute chronic or healed The acute stage is suppurative Lesions are usually benign and heal Principal clinical features are pain, tenderness over kidneys, dysuria and pyuria Inflammation may persist for years or finally heal The entire kidney is usually involved As more and more tissue is destroyed and replaced by fibrous tissue the kidney shrinks If hydronephrosis is present the kidney may be enlarged rather than contracted The pyelonephritic scar is usually U shaped and dark Both kidneys are commonly involved but the disease may be unilateral. Only recently was it recognized that in the chronic stage lesions are usually nonsuppurative and need not be associated with pyuria

Important changes occur in tubules and arteries Convoluted tubules undergo atrophy and polymorphonuclear leukocytes may be seen Glomeruli of affected nephrons are also involved, adhesions develop between tuft and capsule there is periglomerular fibrosis and the glomeruli become hyalinized and finally disappear Such widespread destruction of nephrons results in renal insufficiency Pathologic picture is that of chronic Bright's disease and the patient may die of uremia Arteries in scarred areas show productive endarteritis there is hyperplastic sclerosis in arterioles Inevitable

(3) Canad M A J 47 128 133 August, 1942

of children is 600 000 in 12 hours and of adults 500 000 The normal count for casts is from 15 000 for children to 5 000 for adults The urinary sediment showed the largest number of erythrocytes in the children observed over the longest periods i e 20 17 and 16 years re spectively In two children there was an increase in urinary casts

Also described are the beneficial effects on the nephrot ic syndrome of an acute infection especially measles during an edematous phase This has been noted by Schick Tenzer and Stross and others However an acute infection may be detrimental as there often is a resultant sepsis pneumonia or peritonitis The progno-sis for patients with such complications may be improved now that they are usually treated with chemotherapy and intravenous amino acids

In three children a remarkable temporary improve ment was seen after an acute infection In one improve ment followed acute tonsillitis and in the other two measles Diuresis occurred with loss of edema Albumin uria was considerably reduced or disappeared for sev eral months In one child edema recurred after three months and the child subsequently died of peritonitis two years later In the second child now aged 10 edema recurred for a time He is at present clinically well The third patient now 19 has no subjective symptoms but has an intensive increase in the number of erythrocytes and casts determined by the Addis count

The authors do not recommend that a child in the edematous state should be directly exposed to measles or other acute infections for it has been their experience that patients who have the classic symptoms of chronic glomerular nephritis with edema show no improvement after acute infections

Twelve necropsies have been performed The chil dren usually died from a secondary infection which started from 1 month to 3½ years after onset of the original symptoms The clinical course gave no indica

symptoms are caused by a disturbance of protein metabolism Schick and Addis suggested that the source of this protein disturbance may be in the liver

If lipid nephrosis is accepted as a distinct clinical entity it is rather infrequent In over 20 years, Herman Schwarz, Jerome L Kohn and Samuel B Weiner[4] (Mount Sinai Hosp New York City) have made such a diagnosis for only 40 children In that same period over 400 children with acute or chronic glomerular nephritis were observed Twenty two of the 40 patients have died Eight have been followed for 7 to 20 years, and six of these are aged 15 or older

In 1935 Schwarz and Kohn reported on 15 years' observation of some of these children, stating that there had been an apparent cure in some However, further observation revealed a distinct rise in blood pressure during early puberty in several of the children They have otherwise remained clinically well This rise in blood pressure both systolic and diastolic was higher than that sometimes noted in normal puberty During normal puberty the systolic pressure may rise to 135 mm but the diastolic pressure stays at 65 80 mm The blood pressure was increased at some time in all eight patients observed over a long period In four of these, it has returned to normal and has remained so for several years In one patient aged 17 observed for 13 years the blood pressure is 190/120 Another aged 19 observed 17 years has a blood pressure of 150/90 One patient now 23 had a persistent blood pressure of 150/90 Twice during early pregnancy she has had miscarriages Within the last few months the blood pressure has returned to normal

Addis counts were made recently for seven of the children followed over seven years In four the erythrocyte count was definitely high in all but one of the others there was a slight increase above normal The limit of normal for erythrocytes in the urinary sediment

(4) Am J Dis Child 6 3 5 363 March 1943

of which is unknown Most patients with increased arterial pressure during pregnancy belong to the group of essential hypertension

Experimental renal hypertension has been produced by clamping the renal artery and by establishing diffuse fibrocollagenous perinephritis The resulting syndrome varies from mild to severe hypertension and from entire preservation of renal excretory function to deepening uremia The arteriolar pathology of both benign and malignant forms is nearly coincident with that observed in man There are similar parallelisms in other phases of cardiovascular physiology notably in maintenance in both states of normal levels of cardiac output and peripheral blood flow The similarity is so pronounced that participation of the kidney in the genesis of essential hyperten ion is highly probable

Application of the determinations and concepts of renal function based on use of diodrast and inulin has disclosed that most hypertensives show some reduction of renal blood flow and that this reduction is associated with high filtration fraction i e evidence of increased intraglomerular pressure and therefore of efferent arteriolar constriction This effect is also caused in normotensive human beings by angiotonin injection which fact further links angiotonin to hypertension When the renal blood flow in hypertensives is analyzed in terms of volume of blood perfusing the residually functioning tubular areas it is found that some hypertensives show relatively normal blood flow levels and this accords with the fact that hypertension and normal renal perfusion may occur together experimentally In seeking an explanation it is found that hypertensives show evidence of increased afferent arteriolar resistance (due possibly to arteriosclerosis and vasoconstriction) and increased efferent arteriolar resistance (due to constriction as by angiotonin) and that maintenance of renal blood flow within physiologic ranges in some patients is due simply to the balance between increase

tion of the extent or intensity of the glomerular changes. At some time during the illness of most of these children there were found a moderate increase in blood pressure, slight nitrogen retention occasional casts and a rare red blood cell in the urine

The histologic changes observed in the kidneys varied in accordance with time of onset of the first clinical symptoms (1) In seven children on whom necropsy was done one year or less after onset of symptoms, the glomeruli showed either no pathologic changes or slight congestion of the capillary loops (2) In five children who died one year after onset of symptoms the glomerular changes could be divided into two groups (a) glomerular nephritis with some interstitial scarring and obliteration of some glomeruli was found in two children This was not as extensive as that seen in a typical progressive glomerular nephritis (b) In the other three children there was a definite thickening of some of the glomerular capsules An occasional tuft showed evidence of swelling and was adherent to the capsule At all necropsies the convoluted tubules showed swelling of the lining cells with vacuolation These changes have been described by Wolbach and Blackfan and others in both the glomeruli and the tubules

The authors conclude that most of these patients had glomerular nephritis from onset The clinical expression represented in the nephrotic syndrome would then be a phase in the life cycle of the disease

Renal Aspects of the Late Toxemias of Pregnancy are discussed by A C Corcoran[5] (Indianapolis City Hosp) The vascular toxemias of pregnancy are divided into those not dependent on pregnancy and those dependent directly on pregnancy

The first group hypertension in pregnancy represents in nearly every case a phase latent or apparent, in the development of essential hypertension This disease forms a definite thou h protean syndrome the origin

(5) West. J Su g 50 6 2 630 Decembe 1942

cases renal blood flow remains within normal limits Since arterial pressure is at the same time increased it must be assumed that renal resistance probably in both arterioles and capillaries has been greatly increased In severe cases in which various degrees of cortical damage may occur renal blood flow and tubular mass may also diminish though to a less degree

On the basis of the characteristic lesions this change must be considered a functional expression of the swelling of the glomerular basement membrane characteristic of eclamptogenic toxemia Rapidly after delivery the inability of the glomerular capillaries to transmit water returns to normal and filtration rate rises while blood flow is unchanged Since blood pressure has not entirely returned to normal at this time maintenance of normal rather than increased renal blood flow suggests a residue of increased renal resistance Later at six months post partum both renal function and blood pressure may be entirely restored to normal or essential hypertension has developed If hypertension is present renal blood flow and tubular mass will usually be reduced while filtration rate because of efferent arteriolar constriction will tend to remain normal Stated in terms of routine clinical testing there will be some failure to concentrate urine but urea clearance will be normal Chesley has observed that in post toxemia hypertension the tendency to maintain high filtration fraction is not as great as in uncomplicated essential hypertension possibly because of residual glomerular damage Since hypertension develops in animals from minor renal changes such permanent renal disease as may result from protracted eclamptogenic toxemia might serve as the origin of permanent renal hypertension Evidence on this point is incomplete and it may be that the post toxemic hypertensive patient is one whose eclamptogenic toxemia represented the liability of this state characteristic of essential hypertension

Renal Blood Flow Glomerular Filtration Rate and

of the arterial pressure and an increased renal resistance

Eclamptogenic toxemia is a unique disease Its cause is most likely associated with the uterine contents Various syndromes associated with pregnancy occur in animals but none of these fulfil all the characteristics of eclamptogenic toxemia Resemblance is much less complete than that of experimental hypertension to clinical hypertension of human beings This point is emphasized because of the curious relationship between experimental renal hypertension and pregnancy in dogs and rats In these animals blood pressure drops toward normal as term is approached and returns to hypertensive levels after delivery Similarly onset of renal hypertension is delayed in pregnant animals This protection does not depend on any secretion of hypothetical angiotonin inhibitor from the fetal kidneys into the maternal circulation since pseudopregnancy with deciduoma likewise lowers the arterial pressure of hypertensive rats

In contrast to these results a series of studies have seemed to indicate that pregnant animals are especially susceptible to the effects of severe renal ischemia in that they readily develop hypertension, proteinuria, hematuria and convulsions This syndrome is apparently identical with experimental malignant hypertension as it occurs in nonpregnant animals Although this experimental malignant hypertension is quite similar to malignant hypertension in human beings, clinically malignant hypertension and eclamptogenic toxemia are widely different It therefore seems unlikely that eclamptogenic toxemia is due to the coincidence of renal ischemia and pregnancy This contrast between eclampsia and malignant hypertension is borne out in the renal functional changes of the two conditions

Eclamptogenic toxemia whether eclamptic or preeclamptic, is characterized by decreased rather than increased extraction of water from the blood in the glomerulus i e decreased filtration fraction In most

and children presumably because they have as yet poorly developed perinephric tissues In adults age incidence differs with the type of abscess Most cases of simple perinephric abscess occur between 25 and 35 years whereas complicated perinephric abscess occurs most commonly in the late fourth and fifth decades In this study of 66 patients the ratio of males to females with simple perinephric abscess was 2½ 1 In the group with abscess secondary to renal calculi and pyeloneph ritis however the ratio was reversed Five patients all males presented abscess secondary to pyonephrosis Simple perinephric abscess was nearly twice as common on the right side as on the left Complicated lesions how ever, were encountered on one side as frequently as on the other

Diagnosis of perinephric abscess is made by integra tion of data obtained from history physical examina tion and laboratory studies Early history may contain no specific complaints or may reveal a skin infection or severe upper respiratory tract infection several days or weeks previously Anorexia easy fatigability and night sweats are common early complaints A history of chills and fever is common Weight loss is frequent

Pain is the most common and sometimes the earliest specific symptom It is never colicky but may vary in intensity In some patients it is elicited only by motions of the trunk or on deep breathing or coughing In some it is relieved by flexing the thigh Location of pain is varied. It is most commonly situated in the loin but may radiate to the upper abdominal quadrant par ticularly in cases of abscess secondary to renal calculus or to the lower quadrant in which cases simple perineph ric abscess may be confused with appendicitis or ap pendical abscess In this series nausea and vomiting were common only in cases of abscess secondary to chronic renal disease

Urinary symptoms are uncommon in simple peri nephric abscess When such symptoms are present they

Degree of Tubular Reabsorption of Glucose in Renal Glycosuria Meyer Friedman Arthur Selzer, Jerome Sugarman and Maurice Sokolow[6] (Univ of California) report studies which indicate that the effective renal blood flow glomerular filtration and filtration fraction are within normal limits in the individual with moderate renal glycosuria These observations also indicate that whereas tubular reabsorption of glucose in the glycosuric patient is less than that found in the nonglycosuric individual at moderate plasma concentrations of glucose (100 200 mg per cent) this comparative diminution in reabsorption in the glycosuric subject disappears at higher plasma concentrations of glucose In fact, it would appear as if the glycosuric individual absorbs glucose contained in the tubular fluid more efficiently than does the nonglycosuric individual at high plasma concentrations of glucose This makes it difficult to assume that a serious organic or physiologic derangement is present either in the kidney or elsewhere in the patient with moderate renal glycosuria for a fundamentally deranged organ would not be expected to perform abnormally when not under stress and normally when under considerable stress.

Perinephric Abscess is discussed by F A Simeone[7] (Harvard Univ) It is a suppurative inflammatory lesion of the perinephrium and is always secondary to infection elsewhere Lesions which have reached the perinephrium from distant foci via hematogenous or lymphatic routes are designated simple perinephric abscess Those reaching the perinephrium by direct extension from diffuse pyelonephritis or pyonephrosis or by direct or lymphatic extension from adjacent or nearby foci are called complicated perinephric abscess

Perinephric abscess is not rare Simeone reports that about four cases occur annually on an active surgical service of 100 beds The disease is uncommon in infants

(6) Am J M S 204 229 July 1942
(7) Arch Su g 45 4 4-44 Sept mber 194

with abscess due to pyelonephritis presented a palpable mass without visible swelling in the flank Occasionally, edema and tenderness were observed in the skin and subcutaneous tissue overlying the mass Of special interest is the fact that a large proportion of the palpable masses moved with respiration Abscesses in other locations such as appendical abscesses are usually fixed In cases of perinephric abscess mobility of the mass probably indicates the presence of relatively free layers of paranephric fat

Perinephric abscess may exist in the absence of any abnormality in the roentgen film or may be absent in the presence of one or more characteristic signs

Simeone emphasizes the importance of adequate drainage of perinephric abscess with as little derangement as possible of the body defenses When nephrectomy is indicated it is most safely done as a secondary operation

Renal Concentration Test Using Solution of Posterior Pituitary Harry C Wall[8] (M C A U S) compared this test of Sodeman and Engelhardt with Fishberg s renal concentration test in the study of a large number of persons with and without renal impairment The test with solution of posterior pituitary is done on the unprepared patient After he has voided 0 5 cc solution of posterior pituitary (10 units) is injected subcutaneously No food or fluid is allowed during the two hour period of the test The urine is collected in one and two hours and the higher specific gravity is recorded Six normals gave values of above 1 022 Forty three patients with hypertension or hypertensive heart disease but without renal impairment had values above 1 020 in close similarity with the Fishberg test

Fifteen patients with definite impairment of renal function including nine with malignant hypertension and two with chronic glomerulonephritis had maximum values for specific gravity below 1 020 in both the Fish

(8) A h. Int M d 71 454 459 April 1943

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Patients with perinephric abscess look acutely ill particularly those with simple abscess In the group with complicated abscess the picture is more one of chronicity and debilitation owing to the combined effects of prolonged sepsis and renal insufficiency Night sweats are the rule the skin presents a pasty color Patients with the acute type of abscess are apprehensive those with complicated perinephric abscess are often apathetic Toxicity and prostration characterize the former group, wasting apathy and even coma characterize the latter Patients with complicated abscess seen during an acute exacerbation of nephric and perinephric infection may however show a degree of toxicity equal to that of patients with acute simple perinephric abscess

The degree of fever in these patients is variable Morning temperature is sometimes normal but it rises in the afternoon and evening to 102 106 F It is generally not spiking however except during the early phase of the disease—probably before inflammatory fixation has occurred Pulse rate may be as high as 140 it is seldom below 90

Tenderness occurring in the loin flank or at the costovertebral angle is the most common physical finding, being equally prominent in both types of abscess Spasm in these areas is common in patients with simple perinephric abscess but except in the cases secondary to juxtarenal disease is not as prominent in patients with complicated perinephric abscess

Visible swelling of the loin was observed in 21 of the 34 cases of simple perinephric abscess in 6 of the 12 cases secondary to renal calculus in 3 of the 8 cases due to pyelonephritis without calculus and in 3 of the 7 cases complicating juxtarenal disease A distinct mass however was palpable in only some of these i e in about a third of the cases of simple abscess and half of the cases due to renal calculus Each of eight patients

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renal efficiency hematuria proteinuria and moderate rise in arterial pressure (2) The chronic phase is characterized by edema of hypoproteinemic origin slow progressive loss of renal efficiency proteinuria moderate hematuria and often moderate or marked hypertension (3) The terminal phase is characterized by rise toward normal of plasma proteins and substitution of the edema of heart failure for the hypoproteinemic edema reduction in renal efficiency to below 20 per cent of normal urea clearance polyuria often with diminished excretion of protein hemorrhages exudates and papilledema of the eyegrounds often marked rise in blood pressure acidosis heart failure itching and finally convulsions and coma

The respective aims of treatment in the three phases are (1) to prevent the disease from becoming chronic (2) to maintain the patient s tissues against the ravages of a chronic wasting disease (3) to make exitus as easy as possible

Acute Phase—Onset may be sudden and stormy or insidious Patients with sudden onset have the better prognosis Edema usually of the face and hands is probably caused by increased capillary permeability It requires no treatment but calls attention to onset of a serious disease

The infection which usually precedes the onset is usually due to hemolytic streptococci occasionally pneumococci and more rarely the staphylococci These infections should be treated with sulfonamides, with blood level at 10 mg per cent for sulfanilamide and 5 7 mg per cent for sulfapyridine Precautions should be taken against formation of acetylated sulfonamide calculi in the kidneys Except for emergency procedures surgery should be postponed

Absolute bed rest is essential Room temperature should be kept constant at 76 to 78 F The patient should wear warm pajamas preferably with socks and nursing care should be that of an acutely ill patient

berg test and the test with posterior pituitary solution The comparative results were extremely close, the greatest variation being 0 004

This test seems to be as reliable as the Fishberg test *and presents several advantages It eliminates the necessity of prolonged fluid deprivation* It is useful in office *practice, saving the patient an extra trip and the necessity* of carrying several bottles of urine Another important advantage *is its usefulness in the presence* of a reservoir of fluid in the form of ascites or edema, making restriction of fluids impossible In such a case prompt estimation of renal function can be obtained Wall withholds mercurial diuretics from patients who are unable to concentrate urine to 1 016 If a patient with congestive heart failure shows good concentration on testing even though he has nitrogen retention, it is safe to use mercurial diuretics

The mechanism of the antidiuretic action of solution of posterior pituitary is discussed by Goodman and Gilman The site of action is thought to be the loop of Henle This antidiuretic effect is essential for physiologic reabsorption of water by these cells Solution of posterior pituitary will inhibit water diuresis but xanthines and mercurial diuretics counteract this antidiuretic action and should therefore be omitted before using the posterior pituitary test of renal function

Contraindications for this test are pregnancy and coronary heart disease especially acute myocardial *infarction* In the presence of angina pectoris without recent infarction the test should be used with extreme caution

Treatment of Bright s Disease According to Irvine H Page[9] (Indianapolis City Hosp) the three stages of Bright s disease must be clearly differentiated as their treatment aims differ (1) The acute phase is characterized by *edema probably inflammatory* the occurrence of an infectious process rapid reduction of

(9) J Missouri M A 39 306 310 Octobe 194

Since lymph flow is rapid even when edema fluid is accumulating it is desirable to maintain it at a high level preferably by massage and exercise When the patient is in bed the limbs should be slightly elevated to aid retrograde lymph flow

Large amounts of protein lost in the urine must be replaced by protein feeding Optimal daily amount for adults is 70 100 Gm children require 3 2 Gm per Kg body weight Animal proteins should predominate Flavored casein drinks offer a simple mode of administration Plasma proteins may or may not rise significantly as a result of adequate protein feeding Whatever the response patients should be maintained on the diet because they feel better and do not exhibit the malnutrition evident on protein poor diets There is no contraindication to administration of usual amounts of fat and carbohydrate and the diet should also be supplemented with vitamins

Terminal Phase—The aim of therapy in this phase is to treat symptoms as they arise and to maintain electrolyte and water balances as near normal as possible Nothing is gained by an enforced dietary regimen Usually a diet containing only 30 40 Gm protein is adequate the rest will be cared for by the desires of the patient Often a liqueur or wine taken shortly before meals aids appetite

Care should be exercised in salt restriction During the terminal phase the kidneys inability to concentrate urine causes polyuria resulting in loss of large amounts of salt This loss if not replaced may lead to hypochloremic uremia Occasionally administration of salt leads to temporary recovery with prolongation of life for as much as 18 months Heart failure however contraindicates its use In general salt should be so administered as to maintain a normal blood chloride level 4 Gm per day is usually adequate Sufficient fluids should be given to insure adequate urine flow

Retention of fixed acids loss of base by vomiting and

Dietary management is unimportant the first few weeks since the patient has little appetite Later, adults should receive 40 60 Gm mixed vegetable and animal protein and children, 2 3 Gm per Kg body weight Vitamins A, B complex C and D should be given in increased amounts Salt and water intake should not be limited unless hypoproteinemic edema or heart failure is present

Convulsions may be controlled by 250 cc of 50 per cent sucrose intravenously given very slowly if heart failure is impending Magnesium sulfate (20 cc of 10 per cent solution repeated several times) may be used. Given intramuscularly in doses of 0 3 cc of a 25 per cent solution per Kg body weight it has value in preventing convulsions and may be repeated in four hours Removal of 15 to 20 cc spinal fluid is useful If convulsions continue 3 gr pentobarbital sodium may be given intravenously

Chronic Phase —Edema is related to hypoproteinemia salt and lymph drainage In the stagnation edema of cardiac origin drainage of extracellular fluid back into the blood is abnormally slow while in nephrotic edema it is abnormally fast even when the edema fluid is accumulating It is extraordinarily rapid in periods of diuresis

Treatment of nephrotic edema depends on correction of the causal factors Restriction of salt is imperative Adults should excrete not more than 2 Gm salt daily and children less than 1 Gm gaged by weekly analysis of urinary chlorides Restriction of water is unnecessary Diuretics are of limited value because they seldom correct the basic cause However acid forming salts may aid sodium excretion Daily dosages of 8 10 Gm ammonium nitrate and 10 12 Gm potassium nitrate may be given over a long period if the patient is under observation Potassium nitrate is generally preferable The drug should be administered in 0 5 Gm enteric coated pills.

therapeutic agents are few and for the most part represent merely replacements of normal body constituents

To maintain health, the body must have at least (1) sufficient water to provide a urine volume of about 1 000 cc daily (2) sufficient calories to maintain weight (3) about 1 Gm protein per Kg body weight per day and (4) essential minerals and vitamins In disease these requirements will not be decreased in fact the requirements of some may be greatly increased In health the caloric requirement can readily be established by following changes in body weight in response to a diet of varying caloric content In patients with nephritis it is frequently impossible to estimate the adequacy of caloric intake by such changes

Water balance cannot be interpreted by the difference between fluid intake and urine output Under most circumstances it is impracticable to make the elaborate measurements necessary for its accurate determination but there are fairly reliable clinical signs that indicate changes—increasing edema dry skin and tongue enophthalmos etc

Edema is almost totally dependent on sodium retention For the patient with nephritis quantities of sodium chloride as small as 2 to 5 Gm daily may present a tremendous excess for renal excretion and induce an effect equivalent to 20 to 30 Gm daily in normal subjects

Patients with nephritis can no longer conserve base as efficiently as normal subjects since the ability of the kidney to form ammonia from urea may be limited Sodium and other fixed bases are drawn from the body and excreted to help neutralize acid end products excreted by the kidney This may result in severe depletion of the alkali reserve of the body Two approaches are available to conserve the base reserves (1) decreasing the acid ash of diet by ingesting a diet of neutral or alkaline ash composition and (2) giving an excess of alkali (preferably sodium) to provide for the in

decreased formation of ammonia by the kidneys lead to acidosis which increases the nausea and vomiting of uremia and causes dyspnea Acidosis should be obviated by administration of alkali in repeated doses of 3 to 5 Gm orally If necessary sufficient bicarbonate may be given intravenously to restore the normal alkali reserve Iron may be given for anemia, but gastric disturbance should be avoided Heart failure during uremia should receive the orthodox treatment based on adequate digitalization and moderate fluid and salt restriction Diuretics are useless

Convulsions may be controlled by hypertonic glucose intravenous barbiturates or slow intravenous injection of 500 cc of 2 per cent magnesium sulfate For itching, Page uses pine tar ointment U S P obtundia cream and ergotamine orally (1 mg thrice daily)

Nausea and vomiting are difficult to treat but their severity is lessened if electrolyte balance is maintained Glucose administered intravenously also aids in their prevention moderate exercise and fresh air reduce them Some patients find that cracked ice is soothing Bismuth subnitrate 0 65 Gm plus sodium bicarbonate 1 3 Gm may aid in their alleviation

Physiologic Considerations in Treatment of Nephritis According to George W Thorn[1] (Harvard Univ), much of the confusion surrounding treatment of renal insufficiency would be obviated by a simple therapeutic plan based on consideration of the agents required to correct the principal disturbances in body chemistry and physiology rather than a plan dictated by the nature of the pathologic renal lesion Such an approach necessitates familiarity with the chemical and physiologic changes that may be expected to occur in impaired renal function Quantitative and qualitative considerations require attention since patients with kidney disease are unable to compensate adequately for an excess or a deficiency of the indicated therapeutic agents These

(1) New E gl nd J Med 229 33-48 July 8 1943

over the maximum obtained by fluids orally if glucose solution is given intravenously and that further increases can be obtained if normal saline infusions are used instead of glucose Until disproved it would appear advantageous to use these solutions parenterally in patients with azotemia without edema or impending cardiac failure

In nausea and vomiting it may be possible to administer water by rectum otherwise fluids and nourishment must be given intravenously or subcutaneously Provision of 1 000 to 1 200 calories and 25 50 Gm protein may be considered to meet minimal basic requirements under these circumstances Vitamin preparations may be given parenterally Because of the large quantity of glucose solution needed water requirements are easily met Glucose administration intravenously should not exceed a rate of 1 Gm per Kg body weight per hour for optimal utilization When fluids are forced in patients with azotemia continued treatment may result in a striking fall in the serum level of sodium and chloride a decrease in the plasma volume and consequently dehydration and an increase in azotemia Thus there is a necessity for providing sodium chloride in small quantities at least during such periods of active diuresis

With these considerations in mind the effective physiologic therapeutic agents for use in treatment of the metabolic disorders associated with renal insufficiency include

Water
Minerals
  Sodium chloride
  Sodium bicarbonate and sodium lactate
  Aluminum hydroxide
Glucose solutions
Solutions containing protein
  Albumin
  Plasma
Whole blood
A diet containing the basic nutritional requirements for health

All that can be accomplished will be accomplished with these simple agents The problem is to match correctly the disturbances in function with the proper quan

creased renal needs of fixed base The first approach may be used at all times, the second is usually contraindicated in edema

One of the most characteristic disturbances in metabolism associated with renal disease is hypo albuminemia Since in most cases it is not possible to obtain a striking increase in serum albumin level with high protein feeding or amino acids orally or intravenously serum albumin administration is the only effective means of compensating for this deficiency To maintain nitrogen balance and to attempt to increase the serum albumin level use of one or more of the following nitrogen containing preparations might be considered protein by mouth amino acid by mouth amino acid by vein albumin intravenously plasma intravenously and whole blood intravenously Adequate protein by mouth is of course indicated in all patients who are not nauseated or vomiting Those with normal blood urea level may be given 2 3 Gm protein per Kg body weight with advantage Those with elevated blood urea nitrogen will do better on a diet restricted to 0 5 to 1 Gm protein per Kg Oral administration of amino acid solution has been recommended, but there is little indication for its use if albumin or plasma solutions are available If parenteral therapy must provide all nutritional requirements for longer than one week administration of amino acid solutions is indicated At present, a solution of albumin has two advantages over a solution of concentrated plasma it can be prepared with a relatively low sodium chloride content and it has a higher colloid osmotic pressure Transfusions of whole blood provide hemoglobin in addition to plasma proteins and are the only effective treatment for the anemia so often associated with renal azotemia

In treatment of patients with azotemia without edema forcing fluids is particularly advantageous in reducing the accumulation of metabolites in the blood However studies in dogs reveal that the rate of urine flow and the glomerular filtration can be appr- -reased

cur only in cases with extensive glomerular involvement There is a decrease in plasma volume

Since the renal lesion cannot be attacked directly some means of eliminating sodium chloride and water from the body through the urinary tract must be employed Salt and water intake must be restricted The therapeutic regimen consists of dietetic and diuretic measures which restore the physico electrolytic balance

The diet contains 100 125 Gm protein daily It is salt free except for salt naturally contained in the food and contains 1 000 1 500 cc fluid If the patient s edema free weight is normal the diet should furnish about 2 000 calories It should be supplemented by vitamin concentrates

Diuretic agents are of two types (1) those which have direct action on the kidneys such as mercurial preparations potassium and ammonium salts caffeine derivatives and concentrated dextrose solutions (2) those which act by affecting the colloidal osmotic pressure of the blood such as whole blood or plasma and acacia The latter produce diuresis by increasing plasma volume and by promoting a saline diuresis as well as by raising colloidal osmotic pressure

The authors report 12 cases 10 of which are essentially similar In these the diet yielded 2 000 calories daily and contained 100 125 Gm protein and 800 1 200 cc fluid No salt was added Each patient received 9 Gm potassium nitrate daily and was given iron and vitamin concentrates as needed Each patient also received a minimum of three intravenou injections of 500 cc 6 per cent acacia in a 0 06 per cent solution of sodium chloride at one or two day intervals In some cases more acacia was needed to produce the desired effect The serum acacia concentration was determined one day after injection if it was 2 Gm per cent or more further acacia treatment was not given Otherwise administration of acacia was continued until the patient was free from edema and the serum acacia level was satisfactory Two of the 10 patients received this treatment in the absence of edema

tity of the indicated agent Although the extent and progress of the underlying renal disease is the ultimate factor in prognosis, proper therapy may provide time for healing to take place in patients with an acute process and may rehabilitate for months and even years an appreciable number of patients suffering from the effect of extensive and permanent impairment of renal function

A quantitative outline of therapy to correct various specific metabolic disturbances is presented

Treatment of Edema of Renal Origin is described by Henry J Lehnhoff Jr and Melvin W Binger[2] (Mayo Clinic) The patient with nephrosis or the nephrotic state of chronic glomerulonephritis has as his predominant symptom edema which is characteristic of this clinical entity When the nephrotic features predominate hypertension with its accompanying symptoms is rarely present Renal function is usually good there usually is no retention of nitrogenous matter in the blood, and there is little or no anemia Thus except for generalized edema and the symptoms secondary to it the patient usually feels well and if it were not for the edema, could live a fairly unrestricted life

The edema is the result of water retention and accumulation of excess sodium chloride in the tissues These changes are brought about by loss of protein in the urine or dietary protein deficiency or both This results in decreased serum protein with subsequent decrease in colloidal osmotic pressure of the serum and a tendency to edema formation and retention of salt in the tissues

Laboratory findings disclose albuminuria hypoproteinemia and increased sodium chloride in the plasma and tissues The colloidal osmotic pressure of the plasma is decreased Anemia definite hematuria and pronounced retention of nitrogenous wastes are usually absent Hypercholesteremia is present and the basal metabolic rate usually is low Vascular changes are rare and oc

(2) J A M A 121 1321 13 5 Apr 24 1943

secondary to hypertension the cause of which is unknown

Surgical treatment of hypertension by dorsolumbar sympathectomy gave Benjamin Castleman and Reginald H Smithwick[4] the opportunity to examine the kidney grossly through the operative field and to take a biopsy specimen They report their study of 100 cases Average age of patients was 39 and all had had hypertension for about six years

Each biopsy specimen was graded according to severity of vascular disease without knowledge of clinical

CORRELATION OF RENAL BIOPSIES WITH RENAL FUNCTION AND RETINAL VESSEL CHANGES

RENAL VESSELS	CASES	RENAL FUNCTION			RETINAL VESSELS			
		A	Moderate Reduction	Slight Reduction	1	2	3	4
Normal	7		0	0	5	0	2	0
Grade 1	1	17	3	1	9	8	2	2
Grade 2	5	16	6	3	4	10	9	2
Grade	3	19	6	8	8		10	8
Grade 4	14	1	[illegible]	8		4	[illegible]	2
	100	60	0	0	28	29	9	14

data Qualifying histologic findings for five grades are given with the number of patients in each grade Retinal changes were classified in four grades in order of severity Renal function was measured by the phenolsulfonphthalein test Correlation of renal biopsy findings with renal function and retinal vessel changes is shown in the table

In contrast to the almost invariable postmortem finding of well developed arteriolar disease in kidneys of hypertensive patients 28 per cent of biopsies in this study showed no or insignificant vascular disease and 25 per cent only mild changes It is concluded that the morphologic evidence of renal vascular disease in more than half the cases was inadequate to be the sole factor

(4) J A M A 1 1 1 561 61 Ap 17 1943

They had a history of recurrent edema of long duration, however, and treatment was accordingly instituted as a prophylactic measure The others obtained complete relief from edema Three patients required a second series of acacia treatments

Effect of Kidney Position on Renal Blood Flow and Function D J Gabriele[3] (Brooklyn) has demonstrated that renal circulation may be altered by changing the piezometric angle (angle between a tributary and the advancing blood stream in the mother artery) of the renal artery The problem was studied by obtaining pressure recordings from the cannulated renal artery of a dog while the vessel was made to form various angles with the aorta and by performing diodrast clearance tests on several dogs with the renal artery at various angles Results showed considerable reduction of mean blood and pulse pressures when the piezometric angle was relatively acute Friedman and his co workers stated that reduction of mean and pulse pressure is followed by renal vasodilatation and fall in glomerular filtration rate therefore it is assumed that glomerular filtration was also reduced in Gabriele's dogs This is substantiated by microscopic sections which reveal that glomerular capillaries of elevated kidneys appear less filled with blood than those of normal controls The anatomic basis of predisposition to hypertension may lie in the extreme variability of position of the kidney The deranged renal function of uncomplicated late toxemia of pregnancy may result from high elevation of the kidney during gestation depending on body type and muscle tone

Relation of Vascular Disease to Hypertensive State Postmortem evidence of renal arteriolar disease in hypertensive patients dying of renal failure or other complication has led many people to believe that increased peripheral resistance to blood flow caused by generalized arteriolar disease especially of the kidneys is the cause of hypertension Others believe the arteriolar disease to of hypertension Others believe arteriolar disease to be

(3) Am J M Sc 04 7 3 A gu t, 1947

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Renal Vessels	Cases	Renal Function			Retinal Vessels			
		Normal	Mod Red	Sharp Red	1	2	3	4
Normal	[illegible]		0	0	[illegible]	0	[illegible]	0
Grade 1	21	1	3	1	[illegible]	8		2
Grade	25	16	6		4	10	9	2
Grade	33	19	6	8	8		10	8
Grade 4	14	1	5	8	[illegible]	4	[illegible]	2
	100	60	0	0	8	9	9	14

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(4) J A M A 1 1 1 561 61 Ap 17 1943

in producing hypertension and that in many of these and probably others the hypertension antedated the renal vascular lesion, which once established, probably aggravated the hypertension The authors' observations oppose the concept that renal ischemia due to pre-existing renal vascular disease is the cause of essential hypertension in man

Renal Biopsy Studies Correlated with Renal Clearance Observations in Hypertensive Patients Treated by Radical Sympathectomy John H Talbott, Benjamin Castleman, Reginald H Smithwick, Robert S Melville and L J Pecora[5] (Harvard Univ) report that renal clearance studies performed on 20 patients with essential hypertension showed a significant correlation with the microscopic appearance of the respective renal tissues removed for biopsy at the time of sympathectomy, i e the more severe the renal vascular disease, the more reduced were the glomerular filtration rate and the renal blood flow In cases without renal vascular disease or with minimal arteriolar changes, the renal clearance observations were either normal or only slightly reduced Only in the presence of extreme renal vascular disease was renal blood flow seriously reduced

The filtration fraction was normal in seven of eight *cases in which biopsies disclosed either an absence of* renal vascular disease or minimal or moderate changes It was increased in 6 of 11 cases in which biopsies revealed severe or extreme renal vascular disease These findings indicate that constriction of the efferent glomerular arterioles was not present in the early stages of renal vascular disease

Bilateral radical lumbodorsal splanchnicectomy had relatively little effect on renal clearance when measured in the horizontal position Although glomerular filtration was reduced in the immediate postoperative period about 20 per cent within a year it returned to and continued to maintain its preoperative level Renal plasma flow was essentially unchanged

(5) J Clin In e tgat n 2 387 394 Ma 1943

DISEASES *of the* HEART *and* BLOOD VESSELS

WILLIAM D STROUD M D

PART IV

DISEASES OF THE HEART AND BLOOD VESSELS

INTRODUCTION

In this section as during the past 13 years the articles will be found grouped under the headings as outlined in the nomenclature and crite ia for diagnosis of diseases of the heart revised by the criteria committee of the New York Heart Association (Arthur C DeGraff M D Clarence E de la Chapelle M D Cary Eggleston M D Charles E Kossmann M D Robert L Levy M D John B Schwedel M D and Harold E B Pardee M D chairman) This nomenclature and criteria for d agnosis have been approved by the American Heart Association and copies may be obta ned through its main office at 1790 Broadway New York C ty

—WILLIAM D STROUD

ETIOLOGIC DIAGNOSIS

APTERIOSCLEROSIS

Arteriosclerosis with Special Reference to Coronary Sclerosis Timothy Leary[1] (Boston) states that athero sclerosis is responsible for most of the clinically significant arteriosclerosis i e sclerosis of the coronary peripheral and cerebral vessels Atherosclerosis human or experimental cannot occur without visible cholesterol Visible cholesterol except where normally present in tissues (adrenal cortex myelin sheaths testicles and occasionally corpus luteum) is excess cholesterol a chronic irritant lil e silica it provokes growth of con nective tissue

Two types of arterial lesions are associated with the presence of cholesterol (1) Atheroma is a reversible process in youth responsible for the aortic deposits in nurslings and at puberty and in general for superficial lipoid deposited in arteries of the young Cholesterol

(1) M d C pt C d ul r D V l 11 N 10 O t ber No 11 N emb 194

esters appear in foam cells in the subendothelial layer of the intima as in true atherosclerosis The excess cholesterol however is removed from the lesions by fibroblast like cells, in which the cholesterol esters are split the excess cholesterol is dissolved and disappears from the lesion before its chronic irritant properties provoke true atherosclerosis Power to remove excess cholesterol from arteries is lost with advancing age except in the ascending aorta where it may persist into old age (2) Atherosclerosis is the progressive process in which foam cells persist for long periods and excess cholesterol stimulates growth of connective tissue Definite nodules form and increase in size and more cholesterol appears in new accretions of foam cells Nutrition of the large mass of cells by diffusion of plasma is no longer adequate deeper layers of the lesion undergo necrosis and scarring occurs In addition to the typical orange yellow gray and white nodules soft nodules arise so called atheromatous abscesses made up of foam cells with inadequate supporting tissue and inadequate provision for nutrition Necrosis of the foam cells frees the cholesterol esters which split and free cholesterol forms masses of crystallized rhombic plates A better name for these lesions is atherocheuma (mush liquefied)

In rabbits fed cholesterol there is a latent period of several weeks before lesions appear in the aorta By killing the animals during this period Leary showed that ingested cholesterol is brought to the liver and esterified esters collect in excess in liver cells and adrenals, Kupfer cells and similar cells in the adrenals engulf the excess esters and become foam cells escape from the organs through the blood and lymph, pass through the filter of the lungs and invade the aortic *intima* In this way atherosclerosis is produced

Atherosclerosis belongs with diabetes obesity and gout a group of diseases due to inadequate metabolism of food substances and favored by excessive ingestion There is close linkage between diabetes and atherosclerosis Inadequate carbohydrate metabolism seems to be

accompanied by inadequate cholesterol metabolism Hyperthyroidism is associated with little or no atherosclerosis hypothyroidism with advanced atherosclerosis Apparently because of a more adequate cholesterol metabolism (perhaps related to its mobilization during pregnancy and menstruation) women are less susceptible to coronary sclerosis than men and tend to develop the disease later in life

In early life the coronary lesion may be limited to the left coronary artery and its descending branch The fact that the left coronary artery turns at almost a right angle near its site of emergence from the arterial wall and early in its course gives off a large branch at a right angle could account for unusual and excessive stresses The right coronary artery takes almost a straight course from its orifice and does not give off so large a branch early in its course As in other arteries coronary lesions tend to be most common at or near points of branching With age lesions of the right coronary artery are as frequent as those of the left In addition to stretching tensions coronary arteries are also subjected to medial spasm With atherosclerosis and markedly narrowed lumen death may arise from closure of the lumen by prolonged spasm without thrombosis Spasm may also cause rupture of coronary atherocheumas

Advanced coronary sclerosis in Leary s series at 12 and 18 years with coronary deaths in the twenties or thirties demonstrates that atherosclerosis is not a disease of old age However the type of lesion varies with age In youth, excess cholesterol in the lipoid cells which have *invaded the intima provokes a growth of loose connective* tissue usually placed eccentrically with the lumen pushed to one side Because of inadequate nutrition necrosis occurs in parts most distant from the lumen i e near the media A new source of nutrition arises by the growth of capillaries usually from the lumen The inner layers of the thickened intima become well vascularized tissue In fatal cases which usually terminate by thrombosis sections disclose hemorrhages from ruptured capil

laries and associated fibrinoid necrosis extending up to the endothelial layer thus communicating with and causing the thrombus filling the lumen In middle age more collagen is formed and scarring is typical There is usually dense scarring representing repair of more youthful processes Narrowing of the coronary lumen and chronic vascular myocardosis are frequent Relation to hypertension is close Infarcts may arise in persons who have gone through coronary crises who have been hospitalized for some time before dying and whose hearts do not show occlusion of the coronary vessels supplying the infarcted regions The only adequate explanation of this is that coronary spasm has persisted long enough to produce infarction In addition to frank infarcts a so called miliary infarct may occur frequently multiple and marked by acute death of heart muscle without death of supporting tissue which proliferates Thrombosis is less common in fatal cases in middle age than in youth Calcification of vessel walls is common In old age typical lesions are atherocheumas with calcification Occlusion of the lumen is usually due to rupture of an atherocheuma

Coronary occlusion may be symptomless it may cause mild or serious illness sudden death with ventricular fibrillation or death so instant as to suggest immediate cerebral arrest with cardiac and respiratory standstill

There is no evidence that any therapeutic agent will help the metabolism of cholesterol Choline will prevent excessive deposit of neutral fat in the liver and lipocaic supposedly influences cholesterol metabolism Prevention however by substituting vegetable oils (whose sterols are not absorbed through the animal intestine) for animal fats gives more promise Cholesterol stored in tissues as the individual ages and synthesis of the substance should care for the body s needs on a cholesterol free diet

[As so far there are no accepted methods of preventing myocardial infarction—which *apparently* is on the increase —this work of Leary s is definitely important —Ed]

Serum Cholesterol Level ın Coronary Arterıosclerosıs Alfred Steıner and Beatrıce Domanskı (Columbıa Unıv) determıned the serum cholesterol levels of 15 patıents wıth coronary arterıosclerosıs and of 15 con trols at frequent ıntervals for perıods up to two years Average serum cholesterol values for ındıvıdual patıents wıth coronary arterıosclerosıs varıed from 308 to 499 mg per cent wıth a mean average of 355 mg Average serum cholesterol values for the controls varıed from 214 to 334 mg per cent wıth a mean average of 255 mg Thıs dıf ference between the two groups was found to be statıstı cally sıgnıficant

COMPARISON OF SERUM CHOLESTEROL LEVELS IN PATIENTS WITH CORONARY ARTERIOSCLEROSIS AND NORMAL SUBJECTS

CORONARY ARTERIOSCLE OSIS MG P R C NT	NORMAL SUBJECTS MG P R CENT	
°64	176	39
79	1/8	48
94	185	‿50
97	185	50
305	19ɔ	2ᴗ
31°	208	25
ᴗ15	1°	5
315	21	‿59
335	‿15	63
3 5	216	64
4	16	‿70
355	216	78
3ᴗ9	17	9
380	18	314
50ᴗ	0	337

The fluctuatıon of the serum cholesterol level ın the group wıth coronary arterıosclerosıs as measured by the standard devıatıon varıed from 15 8 to 38 8 and averaged 24 8 The fluctuatıon of the serum cholesterol level of the control group varıed from 3 2 to 17 5 wıth an average of 8 7 The ratıo of 2 8 between the average standard devıatıons was found to have statıstıcal sıgnıficance

Sıngle determınatıons of serum cholesterol ın 15 addı tıonal patıents wıth coronary arterıosclerosıs and ın 30 addıtıonal controls present data confirmatory of the long term study (see Table)

( ) A h Int M d 71 397 40 M h 1943

Bacterial Infection

Subacute Bacterial Endocarditis Due to Streptococcus Viridans Carter Smith, H Cliff Sauls and Charles F Stone[3] (Emory Univ) surveyed the present status of previously reported cures and report another cure occurring in a series of 15 cases The table shows that the percentage of reported recoveries has risen sharply since the advent of chemotherapy The highest recovery

Recovery Rates in Subacute Bacterial Endocarditis with Different Forms of Therapy (from All Medical Literature)

	Cases	Recoveries
Nonspecific treatment of spontaneous recovery	634	6 (1 %)
Chemotherapy alone	198	1? (6 %)
Chemotherapy with heparin	43	5 (11 5%)
Chemotherapy and hyperthermia	[illegible]	4 (16 %)
Chemotherapy and intravenous typhoid	?1	4 (0 %)

Only group studies are included Isolated reports of cases in which recovery occurred are omitted because the percentage of recovery could not be estimated

rate (20 per cent) was obtained in 21 cases with sulfonamides combined with hyperthermia produced by typhoid paratyphoid vaccine Clinical trial on larger groups of patients of combined sulfadiazine and intravenously administered typhoid paratyphoid vaccine should be carried out so that more decisive conclusions may be reached concerning this regimen Surgical ligation must be considered for patients having patent ductus arteriosus associated with subacute bacterial endocarditis

[The most important factor in treatment of this condition appears to be early instigation of therapy Unfortunately after 5 years of effort your editor has yet to see a patient cured —Ed.]

Subacute Bacterial Endocarditis George F Dick[4] (Univ of Chicago) reports a case in which recovery occurred following *intravenous use of sodium sulfadiazine*

Man 30, complained of weakness, 22 lb weight loss, anorexia and nausea for one month and pain in the right shoulder for two days One month previously a traumatic infection of the hand had been treated with some success with local sulfanilamide dressings Since then temperature had been 98 4 102 F Several days previously he had severe chills

(3) J A M A 119 478 482 June 6 194
(4) Ibid 1 J 24 ?5 Sept 5 194

and at another time had observed swelling of the ankles

When seen April 20 blood pressure was 128/75 mm Hg and temperature 100 2 F There was a presystolic and systolic murmur over the mitral area and the heart was moderately enlarged Lung fields were clear Blood studies showed 10 500 leukocytes 4,580 000 erythrocytes and 13.5 Gm hemoglobin per cent Urine showed a trace of albumin and an occasional red and white cell Blood culture showed an average of 51 colonies of Streptococcus viridans in each plate Cultures in broth showed typical colonies of gram positive streptococci forming long chains Two days later a second blood culture showed an average of 41 colonies per plate On this day he was given 40 Gm sodium sulfadiazine intravenously in 500 cc water About two hours afterward he had some cramping abdominal pains and a half hour later vomited

Whereas urinary volume for the 24 hours preceding injection was 1,065 cc the following day it was only 215 cc and urine contained some gross blood The second day following the injection the 24 hour urine volume was 15 cc and daily volume continued as follows April 26 50 cc April 27, 25 cc April 28 130 cc April 29 375 cc April 30 947 cc May 1 1 400 cc After this it continued normally

Owing to loss of fluids by emesis he was given intravenous injections of 5 per cent dextrose in saline solution to maintain fluid and electrolyte balance and April 27 he was also given sodium lactate intravenously to maintain normal pH Blood levels of sulfadiazine and urea nitrogen during this period are shown in the table

LEVELS OF SULFADIAZINE AND UREA NITROGEN IN BLOOD

Date	Sulfadiazine		Blood Urea Nitrogen
	Free	Total	
4/23	89 0	90 0	
4/ 4	73 1	81 0	17 9
4/2	56 7	65 9	
4/26	45 9	70 9	35 9
4/[illegible]	37 4	66 9	44 6
4/[illegible]8	8	60 1	44 8
4/ 9	8 0	56 5	[illegible] 1
4/ 0	3 7	47 7	86
5/ 1	15 6	[illegible]9 5	93 7
5/	[illegible]1	9 0	71 4
/ 5	0 5	1 1	49 3
5/11	11 9	13 0	7.3
5/13	12 [illegible]	13 0	4 9
5/15	1 4	13 [illegible]	6 4
5/17	9 9		
5/18	[illegible]0 2		6 9
5/1[illegible]	9 1	9 3	6 5
5/ 0	3 1	3 [illegible]	

Blood culture three days after intravenous injection of sodium sulfadiazine was sterile, as were cultures made May 1 17 and 26

Temperature following injection of sodium sulfadiazine which had previously been 98 6 100 4 F, fell to normal in a few hours, remained normal for five days and during the next six days varied from 100 4 to 98 F After this it again returned to normal and remained so during the following month May 20 a slight diastolic murmur over the aortic valve was heard

By May 5 total sulfadiazine level in the blood had fallen to 1 1 mg per cent Blood urea nitrogen was normal May 8 and he had normal temperature and urine and felt well Although the blood stream was sterile it was decided to give more sulfadiazine to insure if possible sterilization of the cardiac valves Accordingly intravenous injections were given as follows May 8 5 Gm May 11, 8 Gm May 15 10 Gm. May 17 14 Gm This was followed by a total sulfadiazine blood level on May 17 of 39 9 mg After that he received no medication except for a hematinic elixir and a daily dose of digilanid 0 00033 Gm

Six weeks after the drug was given he felt well and had had a normal temperature for a month Sterility of the blood stream as indicated by culture probably indicates that the heart valves are free from living organisms and that they will remain so unless reinfection occurs

Therapy of Bacterial Endocarditis with Massive Dosage of Sulfadiazine Edgar Hull Robert H Bayley and Alice B Holoubel (New Orleans) report four cases in which gross hematuria followed the massive initial dose of 30 or 40 Gm sulfadiazine dissolved in distilled water The patients were previously alkalinized by administration of sodium bicarbonate

Two of the patients who were in good condition when treatment was begun showed hematuria as the only significant toxic effect of the drug but neither patient was cured The third patient who was very ill when treatment was given developed suppression of urine and died of uremia 11 days after the single injection of 30 *Gm* sulfadiazine Necrotizing nephrosis involving principally the collecting tubules was found at autopsy The fourth patient was practically moribund when treatment was

(5) J A M A 9 5 930 *July 31 1945*

given He died 16 hours after administration of 30 Gm sulfadiazine intravenously No renal lesions attributable to toxic effect of sulfadiazine were found at autopsy

Congenital Anomaly

Newer Concepts in the Diagnosis of Congenital Heart Disease based on clinical and angiocardiographic study of 80 patients over 4 are discussed by Marcy L Sussman Arthur Grishman and Morris F Steinberg[6] (New York City) In some cases operative and postmortem data also were available and visualization of cardiac chambers during life after intravenous injection of 70 per cent diodrast permitted a more accurate analysis of cardiac contours and a clearer understanding of disturbed cardiac physiology than were previously available

The following classification was used and cardiac configurations were grouped according to outstanding characteristics (1) enlarged pulmonary artery segment of the cardiac contour (2) normal or small pulmonary artery segment with (*a*) right and (*b*) left ventricular enlargement (3) right aortic arch and (4) dextrocardia

Enlarged Pulmonary Artery Segment —This may appear prominent roentgenographically in atrial septal defect patent ductus arteriosus isolated pulmonary stenosis with dilated pulmonary artery idiopathic dilatation of the pulmonary artery and Eisenmenger s complex

History of recurrent or persistent cyanosis indicates a right to left shunt and suggests Eisenmenger s complex Cyanosis may appear under condition of strain in atrial septal defect and occasionally in patent ductus arteriosus occurring particularly in infancy but is not pronounced while in isolated pulmonary stenosis it is of late onset of moderate intensity and progressive In all conditions of this group dyspnea on exertion and slight bluishness of lips may be present Cardiac failure may

(6) Am J D Child 65 9 936 J 1943

be present continuously in atrial septal defect but is rare in patent ductus arteriosus Subacute bacterial endocarditis occurs frequently with patent ductus but is rare with uncomplicated atrial septal defect

With atrial septal defect, blood pressure may be low and pulse pressure small The heart is enlarged to the left with a forcible apical pulsation displaced to the left, a heaving systolic pulsation over the chest wall, a systolic thrill and perhaps a diastolic shock over the pulmonic area, a decrescendo systolic murmur extending through systole, best heard over the pulmonic area and just below it with a soft blowing diastolic murmur in the same region (Graham Steelle) apical murmurs of mitral disease and a greatly accentuated pulmonic second sound with an almost metallic quality These murmurs are probably due to the dilated pulmonary artery with relative pulmonary stenosis and insufficiency rather than directly to the septal defect They are similar to those of idiopathic dilatation of the pulmonary artery except that apical murmurs are absent A continuous loud harsh murmur with systolic accentuation at the pulmonic area generally associated with a systolic thrill is characteristic of patent ductus arteriosus It may be transmitted over the left ventricle region with its systolic component often audible in the carotid arteries A systolic murmur over the jugular notch is common and the pulmonic second sound is accentuated Pulse pressure is increased because of a low diastolic pressure which occurs when there is considerable aortic regurgitation into the pulmonary artery during diastole Isolated pulmonary stenosis with dilated pulmonary artery is rare A thrill over the second and third left intercostal spaces or diffuse over the precordium is fairly frequent, and a prolonged harsh rasping or blowing systolic murmur maximum at the pulmonic area is often present It is transmitted upward along the pulmonary artery and over the sternum The pulmonic second sound is weak or absent but may be increased and a faint short diastolic murmur may be he left

of the sternum These signs simulate Eisenmenger s complex except that in the latter a diastolic murmur at the base and along the left sternal margin is reported A diastolic thrill may be present and the pulmonic second sound is markedly accentuated

[I have been impressed with the high incidence of patent ductus arteriosus *without* the so called machinery murmur and without a thrill I still feel operation is not indicated in this condition unless there is definite evidence of malnutrition or progressive cardiac enlargement —Ed]

The electrocardiogram may have differential diagnostic value in this group Right ventricular enlargement found regularly in pulmonic stenosis atrial septal defect and Eisenmenger s complex is apt to be associated with right axis deviation often marked Right bundle branch block is not uncommon and abnormal increase in amplitude of the P wave with notching is common Prolonged P–R intervals are not infrequent and T waves may be inverted in leads II and/or III Auricular fibrillation occurs only in atrial septal defect and is more often present when mitral stenosis exists or in older patients In patent ductus arteriosus extreme right axis deviation is unusual

A delay in arm to lung and arm to tongue circulation time is common in right ventricular enlargement and in failure However when these time intervals are equal a right to left shunt is indicated and in this group of lesions suggests transposition of the great vessels as in the Eisenmenger complex There is no indication of a right to left shunt in any other member of this group

Roentgenographically an enlarged often bulging pulmonic segment at the middle left cardiac contour is outstandingly characteristic The contour immediately below the pulmonary artery and above the left ventricle in the postero anterior view ordinarily is concave When the right ventricle and auricle are enlarged as is likely in all conditions of this group except patent ductus arteriosus the heart diameter at the level of this concavity is widened and the junction of the right cardiac and supracardiac borders is elevated Marked cardiac

enlargement to the right is common only with failure Enlargement to the left in the postero anterior view is common The dilatation of the pulmonary artery extends into the hilar vessels which pulsate actively When pulmonary insufficiency is present, organic or relative the pulsation is of the collapsing type, giving an appearance describe as a "hilar dance" This is a feature of atrial septal defect Although pulsation in patent ductus arteri



Fig 56 —Eisenm nger c mplex in b y 16 l ft obl que ang o ard gram three ec d fter i j ct n Op ff t n of ght side f h art and d at d pulmonary a ter y left ventr le and aorta fa tly but d fin tely opacified no pulm n c ten s s gh t sid of h rt mode ately dilated

osus may be prominent it is not collapsing Absence of marked left auricular enlargement is important in this group and when the esophagus appears displaced posteriorly and is compressed as in mitral stenosis, diagnosis of Lutembacher's syndrome is justified provided simple mitral stenosis is excluded Particularly in conditions associated with right sided cardiac enlargement the aorta is apt to be small and the knob absent The Eisenmenger complex is an exception the aorta is

normal in size or dilated In patent ductus arteriosus and idiopathic dilatation of the pulmonary artery the aorta does not appear unusually small

Angiocardiography is of great value in differential diagnosis and proves that a prominent pulmonic segment is due to dilatation of the artery Differentiation from mediastinal tumor or a normal sized pulmonary artery distorted by a mediastinal process may be impossible by any other method In the Eisenmenger com





Fig 57 —Eisenmenger complex ... showing ... dilated pulmonary artery

plex this procedure shows that the aorta receives blood from the right ventricle It is opacified within two seconds after injection immediately after opacification of the right ventricle and simultaneously with visualization of the dilated pulmonary artery (Fig 56) In atrial septal defect a right to left shunt is occasionally demonstrated This is unexpected since the left auricular pressure exceeds that of the right and is explained by the sudden but temporary increase in pressure in the right auricle due to introduction of diodrast A left to

right shunt ordinarily is anticipated and can be demonstrated by continued opacification of the right auricle beyond the time that it should be emptied Practically this demonstration often is not conclusive, since continued right auricular opacification may result from other reasons However, angiocardiography always demonstrates the extreme right cardiac enlargement Even in Lutembacher s syndrome, this dilatation of the right side of the heart dominates the picture and there is no striking displacement of the right chambers by the left auricle (Fig 57) This differs from simple mitral stenosis in which the left auricular dilatation overshadows the right side of the heart and in fact displaces the right ventricle and pulmonary artery anteriorly and cephalad. The aorta is normal in size or small A picture similar to that of atrial septal defect is obtained with isolated pulmonary stenosis Idiopathic dilatation of the pulmonary artery is suggested when pronounced enlargement of the pulmonary artery is not accompanied by the marked enlargement of the right side of the heart characteristic of pulmonary stenosis In these cases the right side of the heart was not markedly enlarged, although in 50 per cent the pulmonary artery was dilated However, in 26 of 27 cases the aorta just beyond the arch showed an abnormality in contour Whereas normally it should be smooth with a gradual decrease in caliber from arch to descending portion in patent ductus arteriosus there is an aortic bulge just beyond the arch on the inner side of the curve probably representing the infundibulum of the ductus In most cases the left ventricle was dilated in varying degrees

Right Ventricular Enlargement with Small Pulmonary Artery —This group includes isolated pulmonary stenosis with a small pulmonary artery tetrology of Fallot cor biatriatum triloculare and transposition of the great vessels with small pulmonary artery

Cyanosis and clubbing are prominent and permanent when transposition is present In isolated pulmonary stenosis cyanosis appears late is usually r [illegible] ve and is

emphasized by exertion A harsh systolic murmur and thrill in the second and third spaces to the left of the sternum occur in pulmonary stenosis The murmur is louder than that heard in tetrology of Fallot and is not conducted into the neck In conus stenosis of the pulmonary artery the murmur is slightly lower In tetrology of Fallot a thrill may be present but it is more common in isolated pulmonary stenosis A systolic murmur of less intensity may be heard over the entire heart but is maximum at the pulmonic area It is transmitted into the neck vessels and may be heard in the left interscapular area presumably due to the over riding aorta With cor triloculare the murmur may be absent and often is not transmitted The pulmonary second sound is diminished or absent

Right axis deviation is characteristic unless complicated by a gross conduction defect However in pulmonic stenosis the axis deviation usually is not so pronounced P waves are often large and bifid Circulation studies are important In tetrology of Fallot the right to left shunt permits injected substances to enter the systemic circulation simultaneously with their entrance into the pulmonary circulation These circulation times therefore although they may be prolonged are equal

Roentgenologically the cardiac configurations may be similar to that described as coeur en sabot ' The heart is enlarged to the left and the apex is lifted The pulmonary artery segment is small The aorta is normal or in the tetrology of Fallot may show dilatation of the ascending portion In pulmonary stenosis dilatation of the right ventricle and auricle may be so great that the waist of the heart below the pulmonary artery segment is widened the right cardiac and supracardiac junctions may be elevated

Angiocardiography permits conclusive differentiation In the tetrology of Fallot the aorta and pulmonary artery are visualized simultaneously usually within three seconds and the pulmonary artery is very small A shunt into the left ventricle may or may not be seen depend

ing on how much blood passes through the interventricular septal defect The right ventricle and auricle are enlarged, but their cavities are not greatly dilated. In isolated pulmonary stenosis both cavities are greatly dilated and the pulmonary artery can be identified as a small vessel with an elongated narrow segment between it and the large right ventricular cavity Coarctation of the aorta is seen with ease because of the concentration of diodrast in the aorta Likewise a right aortic arch may be proved

Left Ventricular Enlargement—This group includes coarctation of the aorta atypical aortic coarctation with absence of left radial pulse aortic or subaortic stenosis patent ductus arteriosus without dilatation of the pulmonary artery "idiopathic" hypertrophy and isolated interventricular septal defect

In coarctation the heart may be normal or slightly enlarged Gross enlargement is apt to be associated with aortic insufficiency The cardiac impulse is forceful and a systolic thrill may be felt over the base of the heart base of the neck and often over the vessels forming the collateral circulation Likewise a systolic murmur loudest at the base may be transmitted along the collateral vessels Murmurs however may be completely lacking When recorded the systolic murmur may be found to extend into early diastole and is maximum at or near the pulmonic area The blood pressure particularly systole is usually increased It is decreased in the legs and may be lower than that in the arms Enlarged tortuous vessels may develop in the scapular area intercostal spaces and course of the internal mammary artery

In atypical coarctation with absence of the left radial pulse significant cardiac findings are lacking The blood pressure in the right arm and that in the lower extremities are in normal relation but that in the left arm is lower than that in the right

The signs in aortic or subaortic stenosis are characteristic The heart may or may not be enlarged A systolic thrill may be felt over the entire precordium but

is usually maximum or localized in the first and second spaces on the right A loud harsh systolic murmur maximum in the second right space, is transmitted along the great vessels and may be heard in the carotid and axillary vessels Blood pressure may be normal or low, and pulse pressure is reduced

Idiopathic hypertrophy is rare beyond infancy unless associated with glycogen disease the heart is enlarged to the left and usually no significant murmurs are heard Isolated interventricular septal defect is also rare, and a loud rough systolic murmur best heard at the left third and fourth spaces with a thrill is characteristic

Electrocardiograms do not help in differential diagnosis Circulation studies are most important if not pathognomonic With aortic coarctation pulse tracings over the radial and femoral pulses show a delay in the femoral pulse wave varying between 0 06 and 0 12 second as compared with the normal pulsation in which the femoral wave precedes the radial There may be a palpable difference in temperature between the extremities the hands being moist and warm and the legs and feet cold With atypical coarctation the coarctation is not great enough to produce a delay in the femoral pulse However the left subclavian artery is completely or partially stenosed and the left radial pulse cannot be felt When recorded there is a noticeable delay before its peak is reached An anacrotic notch is often present over the left common carotid artery and occasionally the innominate artery These findings with a normal relation of femoral and right radial pulses are pathognomonic

Conventional roentgen examination reveals hypertrophy and dilatation of the left ventricle in this group However this may be slight Occasionally with coarctation the narrowed aortic segment just beyond the arch is demonstrated fluoroscopically In more cases indirect evidence of dilated intercostal arteries is afforded by notching of the under surfaces of the upper ribs where

the grooves for these vessels are situated In aortic sten osis, the ascending aorta is described as small and its pulsation quiet However this is not constant

Angiocardiography is of diagnostic value in many of the conditions of this group A long narrowed, deformed aortic segment just beyond the arch is present in coarcta tion and the dilated internal mammary arteries are seen Left subclavian artery stenosis can be shown since this vessel is visualized regularly

Right Aortic Arch—This is relatively frequent and occurs in persons with an otherwise normal heart or with other congenital abnormalities Dysphagia may be the only clinical symptom and is rare Embryologically it results when the right branchial artery instead of the left develops into the aortic arch The latter may be present in a rudimentary form as (1) a so called dorsal diverticulum extending posterior to the esophagus and slightly to the left (2) a rudimentary arch or ventral diverticulum (3) a fully developed left aortic arch (double aorta) which is rare or (4) a left innominate artery simulating an isolated transposed aorta Th aorta may cross from the right to the left of the spine at one or two different levels producing different roentgen findings as follows (1) so-called high cros ing in which the aorta ascends to the right of the spine and crosses to the left behind the esophagus, displacing the latter and the trachea anteriorly (2) so called low crossing, in which the arch and descending aorta are to the right of the spine crossing to the left just above the dia phragm posterior to the esophagus to reach the normally located aortic opening of the diaphragm

Dextrocardia—The following classification is pro posed Type I dextrocardia with complete or partial transposition of viscera (situs inversus) The relation of the heart to the viscera is unaltered, resulting in a mir ror image' of the normal The electrocardiogram shows complete inversion The electrical axis runs from left to right being rotated 180 degrees from normal

Type II, dextrocardia without

and with inversion of cardiac chambers The heart is transposed as in complete transposition the left ventricle lying in front and the right behind The electrocardiogram is of the "mirror image" variety

Type III dextrocardia without transposition of viscera and with normal arrangement of cardiac chambers. The left ventricle lies anteriorly and the right posteriorly The aortic arch presents on the left border and the aorta descends to the left of the spine The electrocardiogram shows a normal electrical axis

Type IV dextrocardia with congenital abnormality of the thorax diaphragm or lungs The chamber arrangement is normal and the electrocardiogram shows a normal electrical axis

Type V acquired dextrocardia

Types II and III usually require differentiation Type II is rare and may be proved during life only by angiocardiography Type III may be suspected during conventional fluoroscopic examination when on the patient's being turned into a slight left oblique position there results an exaggerated but otherwise normal configuration for this position

Prognosis for Children with Congenital Anomalies of the Heart and Central Vessels Life Expectancy in Patent Ductus Arteriosus was investigated by May G Wilson and Rose Lubschez (Cornell Univ) It has been estimated that 1 2 per cent of cases of organic heart disease in adults and 5 12 per cent in children are due to congenital malformations of the heart Incidence among 152 cases of congenital cardiac malformations taken from autopsy reports of the New York Nursery and Child s Hospital and the New York Hospital was greatest in infancy Distribution in these 152 cases was septal defects 38 2 per cent valvular anomalies 24 4 per cent anomalies of the great vessels 19 7 per cent uncomplicated patent ductus arteriosus 10 5 per cent

Analyses based on a selected group of fatal cases are not suitable for determining the hazard for living pa

(7) J P d t 1 330 J ly 1 42

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Analyses based on a selected group of fatal cases are not suitable for determining the hazard for living pa

(7) J P d t 21 3 0 J ly 194

tients with uncomplicated patent ductus arteriosus To estimate life expectancy in congenital heart disease a representative sample of the population observed over a full span of life should be used Opportunity to observe 132 children considered to have congenital heart disease in the pediatric cardiac clinics afforded data suitable

MORTALITY RATE IN CONGENITAL ANOMALIES OF HEART AND CENTRAL VESSELS AMONG 132 PATIENTS OBSERVED OVER [illegible]0 YEARS

DECADE	NO CASES REPRESENTED	OBSERVED LIFE EXPERIENCE PERSON YR	DEATHS†	ANNUAL DEATH RATE %	AV PERIOD OF OBSERVATION IN EACH DECADE YR
A All Patients					
2 9	104	406 5	2	0 49	3 9
10 19	113	71[illegible] 0	5	0 [illegible]0	6 3
20 29	37	174 5	—	—	4 7
30 +	3	[illegible]0	—	—	3
B Patients with Patent Ductus Arteriosus					
2 9	30	10[illegible] 5	—	—	3 6
10 19	38	260 0	1	0 38	6.8
20 29	14	70 0	—	—	5 0
30 +	2	1 0	—	—	0 5
C Patients with Cyanosis					
2 9	17	[illegible]65	1	1 77	3 3
10 19	18	104 0	2	1 92	5 8
20 29	3	[illegible]5	—	—	2.5
30 +	—	—	—	—	—

* Patients observed during any part of indicated decade
† There were four additional deaths two in the first decade one in the second decade and one in the third decade not attributed to congenital cardiac malformation

for such analysis Patients were observed over 20 years average period being 9 years Ages ranged from 2 to 30 There were 7 deaths attributable to congenital heart disease Annual mortality rate (see Table Division A) for observations made in the first decade of life was 0 49 per cent i e a child with congenital heart disease has 1 chance in about 200 of dying before he is 10 For the second decade mortality rate was 0 70 per cent i e a child with congenital heart disease who has survived to the age of 10 has 1 chance in about 140 of dying before he reaches the age of 20 No deaths occurred in this series in the third decade

A separate mortality rate was made for 38 patients with uncomplicated patent ductus arteriosus (see Table Division B) This rate was found to be 0 38 per cent in marked contrast to that obtained for the 24 patients with congenital heart disease associated with cyanosis (Division C) in which it was 1 77 per cent for the first decade and 1 92 per cent for the second In other words a child with patent ductus arteriosus reaching the age of 10 has 1 chance in 260 of dying before he reaches the age of 20 while a patient with cyanosis has 1 chance in about 52 of succumbing in the same decade The annual risk of death is five times as great for persons with congenital heart disease associated with cyanosis The low mortality rate for all the patients with congenital heart disease is reflected in the rate for the 38 patients believed to have uncomplicated patent ductus arteriosus These mortality rates gives a life expectancy in marked contrast to that estimated from any series of selected fatal cases In no instance in this series of 38 patients was there a death due to bacterial endocarditis or cardiac failure There was one unexplained sudden death Three patients were considered to have slight impairment of nutrition and one had a slightly diminished cardiac reserve At last observation (1941) 24 of the patients were between 10 and 20 12 between 20 and 30 and 2 were over 30

In view of the low mortality rate in the authors series from all types of congenital defects and from patent ductus arteriosus surgical intervention in children believed to have patent ductus arteriosus would not seem indicated

Subacute Bacterial Endocarditis Complicating Patent Ductus Arteriosus William A Winn Clara L Hughes and Jewell M Sanders[8] (Springville Calif) report a case of subacute bacterial endocarditis in a woman 45 together with patent ductus arteriosus and mild pulmonary tuberculosis Treatment with sulfapyridine and heparin according to the method of

(8) A n Int M d 18 4 50 Feb ry 1943

tients with uncomplicated patent ductus arteriosus To estimate life expectancy in *congenital* heart disease a representative sample of the population observed over a full span of life should be used Opportunity to observe 132 children considered to have congenital heart disease in the pediatric cardiac clinics afforded data suitable

MORTALITY RATES IN CONGENITAL ANOMALIES OF HEART AND CENTRAL VESSELS AMONG 132 PATIENTS OBSERVED OVER 20 YEARS

DECADE	NO CASES REPRESENTED	OBSERVED LIFE EXPERIENCE PERSON YR	DEATHS†	ANNUAL DEATH RATE %	AV PERIOD OF OBSERVATION IN EACH DECADE YR
A. All Patients					
2 9	104	400 ˌ	2	0 49	3 9
10 19	113	715 0	5	0 0	6.3
20 29	37	1ˌ4 ˌ	—	—	4 [illegible]
30 +	3	ˌ 0	—	—	°3
B Patients with Patent Ductus Arteriosus					
2 9	30	107 5	—	—	3 6
10 19	38	°60 0	1	0 38	6 8
20 _9	14	70 0	—	—	5 0
30 +	2	1 0	—	—	0 5
C Patients with Cyanosis					
2 9	17	5[illegible]	1	1 ˌ7	3 3
10 19	18	104 0	2	1 9	5°
20 _9	3	[illegible]	—	—	2.5
ˌ0 +	—	—	—	—	—

Pat nts observed dur ng any part f indicated de ad

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Rarely instances of effort syndrome are encountered in which the condition does not appear to belong to the neuroses and the effort intolerance under such circumstances is regarded as possibly indicating predisposition to neurosis Predisposition of this kind would typically be followed by development of a neurosis when the subject is under stress and the effort intolerance represents a preneurotic stage

While all the patients complain of effort intolerance it is necessary to assess this on objective tests The respiratory exercise tolerance test is of value as an objective test of the degree of breathlessness when doing light work but it is unpleasant and may tend to focus a patient s attention on his breathing However the technic now used eliminates these objections as far as possible

The unopposed pedaling test eliminates those patients whose anomalies of respiration make them unsuitable for further physiologic study and demonstrates hyperpnea of an unmistakably emotional kind

Fundamental to the study of effort syndrome is the question of why such patients break down when doing heavy work at a much earlier stage than do normal controls Studies of maximal effort with a constant work load have not yet been completed but indications are that the exhaustion point occurs much earlier in patients than in controls and that changes in the lactic acid content and the pH of the blood are so small that physiologic fatigue does not seem to be present

In certain groups of patients with effort syndrome which represent a small percentage of the whole and probably are limited to those who would not be classified as neurotic the point of fatigue occurs earlier than in the controls but is accompanied by changes in the lactic acid content and the pH of the blood which are similar to the maximal figures for fatigue in normal controls

Abnormalities of Amount of the Circulation (Hyper and Hypokinemia) and Their Relation to Neurocircu

Kelson and White, resulted in sterilization of the blood stream and complete recovery The patient has been followed for one year

Effort Syndrome

Effort Intolerance in Soldiers The number of cases of effort syndrome occurring in the British Army has been much smaller in World War II than in World War I One reason for this has been the insistence that strong reassurance by medical officers be given when men first report sick with palpitation etc Maxwell Jones and R Scarisbrick[9] (London) believe that this change of attitude by members of the medical profession is probably the most important single factor in limiting the incidence of effort syndrome The handling by a psychiatrist rather than a cardiologist of such patients with this disorder as do reach a hospital or are sent there for the opinion of a specialist is probably another factor in limiting the spread of the condition in this war Wood a cardiologist after close study of several hundred patients concluded that the condition is emotionally determined in almost all cases

From experience gained in treating and studying a group of 500 patients with effort intolerance the authors feel that the following conclusions are justified

There is no good reason for retaining the diagnosis effort syndrome as the conditions can almost always be placed in the usual psychiatric classification It may however be advantageous to study this mixed psychiatric material primarily from the viewpoint of effort intolerance If this is done a separate classification is needed This the authors have attempted to provide by considering the subjective complaint of effort intolerance and subjective and objective evidences of vegetative lability and anxiety whether generalized related to certain parts of the body or apparently absent Such a classification is an essential preliminary to a more detailed study of effort intolerance and fatigue

(9) War Med " 901 911 No emb r 194

hypokinemia are weak and dizzy they complain of dyspnea on exertion, and about a fourth have repeated fainting attacks Those with hyperkinemia deny weakness dizziness is a minor factor and there is no fainting They seldom consider themselves ill although they are underweight and tend to have tachycardia An experienced clinician inspecting patients with essential hypokinemia has no definite diagnostic impression but patients with essential hyperkinemia are immediately

SYMPTOMS IN ESSENTIAL HYPO AND HYPERKINEMIA

	HypO	HypER
Average age yr	36	3
Deviation from ideal weight lb	+6	—13
Average pulse rate	74	90
Symptoms—Nervous	++	++
Weak	+++	0
Dizzy	+++	+
Fainting	+	0
Dyspnea on exertion	+++	+
Average B M R %	—8	—3
First impression	?	Hyperthyroidism

suspected of having hyperthyroidism and only after repeated estimations of basal metabolic rate is this diagnosis abandoned

Of 22 patients with no circulatory abnormality detected at rest 7 exhibited weakness dizziness and the proneness to fainting characteristic of the essential hypokinemic group The resting circulation although not subnormal was exactly on the lower limit of normal hence these cases are added to the essential hypokinemic group

Fifteen patients had less in common Seven had all their symptoms in attacks considering themselves well and free from symptoms between these episodes But the attacks were of various characters spells of weakness and faintness and attacks of palpitation were most common All these patients were neurotic and in some the neurotic origin of the symptoms was apparent In four patients although circulation was normal when at rest when they arose there occurred an increase in

latory Asthenia and Kindred Diagnoses Isaac Starr[1] (Univ of Pennsylvania) *reports on 68 cases characterized by symptoms referable to the circulation* which could not be accounted for by any abnormality demonstrated by usual procedures such cases are usually diagnosed functional heart disease neurocirculatory asthenia autonomic imbalance sympathicotonia vagotonia etc By ballistocardiographic estimation of cardiac output functional abnormalities of the circulation were discovered in many such cases Similar changes however have also been found in many patients with organic disease Thus hypokinemia (decreased motion of blood) is found in most cases of congestive heart failure In cases of valvular heart disease not in failure the abnormality is often encountered chiefly in those who have been in failure or who are in danger of it In chronic angina pectoris hypokinemia is the rule Over a third of the patients with hypertension show hypokinemia chiefly those with small hearts Persons with severe cases of certain endocrine diseases (myxedema pituitary or adrenal disease) usually have it It is common in convalescence from severe acute infections In Starr's series hypokinemia was found in 26 cases without attributable cause

Hyperkinemia (increased motion of blood) is exhibited by almost all patients with hyperthyroidism without obvious cardiac involvement The hyperkinemia of emaciated persons is partly a matter of definition for their circulations are above normal in relation to body weight Most patients with patent ductus arteriosus had hyperkinemia Twenty of the present series are classed as having essential hyperkinemia since no reason for the abnormality was discovered

A comparison of the clinical picture of the two groups classified as having essential hypokinemia or essential hyperkinemia is given in the table Both consist chiefly of young adults who consider themselves nervous thereafter the similarity becomes less marked Those with

(1) Am J M S 204 573 581 Oct 194

hypokinemia are weak and dizzy they complain of dyspnea on exertion, and about a fourth have repeated fainting attacks Those with hyperkinemia deny weakness dizziness is a minor factor and there is no fainting They seldom consider themselves ill although they are underweight and tend to have tachycardia An experienced clinician inspecting patients with essential hypokinemia has no definite diagnostic impression but patients with essential hyperkinemia are immediately

Symptoms in Essential Hypo and Hyperkinemia

	HypO	HypER
Average age yr	36	3
Deviation from ideal weight lb	+6	−13
Average pulse rate	74	90
Symptoms—Nervous	++	++
Weak	+++	0
Dizzy	+++	+
Fainting	+	0
Dyspnea on exertion	+++	+
Average B M R %	−8	−3
First impression	?	Hyperthyroidism

suspected of having hyperthyroidism and only after repeated estimations of basal metabolic rate is this diagnosis abandoned

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the rate and also in output per beat so that the relation of the circulation in the two positions was profoundly altered It was while the cardiac output was abnormally elevated that these subjects had symptoms such as dizziness and faintness contrary to general expectation. Apparently they have incoordination of the circulation a failure to adapt normally to the needs of the situation.

On the basis of this study Starr proposes subdivision of patients with symptoms referable to their circulation but without heart disease into hypo hyper and normokinetic groups until better knowledge can provide an etiologic classification

Neurocirculatory Disease in the Soldier Harry A Durkin (Peoria) believes that neurocirculatory asthenia should be regarded as a general fatigue state with cardiac or nervous manifestations, either of which may predominate This syndrome is not peculiar to soldiers but may be exhibited by any normal individual when he undergoes excessive physical or emotional stress The significant differential point however lies in the ease with which symptoms may be produced In the extreme case there is breathlessness characterized by a respiratory rate of 40 to 60 per minute The accessory muscles of respiration are called into play facial muscles express distress the alae nasi dilate and the skin becomes pale or dusky Palpitation may be extreme and the heart rate may reach 150 or more Precordial pain varying from a dull ache to simulation of the anginal syndrome is frequent Other symptoms are giddiness excessive fatigue coarse tremors of the extremities sweating and occasionally syncope Blood pressure is usually elevated

This syndrome may arise in three etiologic groups The first two consist of normal individuals who eventually break under prolonged service or who have been weakened by infectious processes These cannot be eliminated in induction examinations but such examinations when properly conducted can screen out members

(2) Ill n M J 8 354 358 No embe 194

of the third group who exhibit certain characteristics which suggest that they will develop symptoms on slight to moderate strain

These individuals exhibit signs of constitutional inferiority either physical or nervous Physically they are poorly developed visceroptotic narrow or flat chested and generally delicate Nervously they are excitable high strung oversensitive and tend to blush and perspire easily They are not adjustable to the stress and emotional conflicts of modern warfare Many of these will be eliminated during routine draft examinations but in such examinations others will be passed only to develop symptoms during training Durkin believes with Lewis that the most satisfactory manner of eliminating these subjects is through the medium of test exercises before induction and through careful follow up observations by physical training instructors during training

Hypertension

Treatment of Essential Hyperten ion by Sympathectomy James Bordley III Morton Galdston and Walter E Dandy[3] present data on 12 patients three to seven years after operation The sole criterion for operation was the presence of incapacitating symptoms In three patients a supradiaphragmatic splanchnicectomy (Peet s operation) was performed and in 9 an infradiaphragmatic splanchnicectomy (Adson Craig s operation) The Peet operation was carried out at first but was supplanted by the Adson Craig operation because the latter permits exploration of the kidneys and adrenal glands and interruption of a large part of the sympathetic supply of the thighs and legs in addition to that of the splanchnic area

Arterial pressure was reduced for 6 to 18 months in four of the nine patients treated by the Adson Craig operation and for 4½ years in one of the three patients treated by the Peet operation Return of arterial pressure to preoperative levels was not accompanied by re

(3) B ll J h H pki H p 7 127 165 M h 1943

generation of the sympathetic innervation of the lower extremities as indicated by sweating and skin resistance tests and skin temperature studies

In a few patients there was objective evidence of regression of abnormal findings in the cardiovascular system during the period of lowered arterial pressure These reappeared after the arterial pressure rose to its previous levels One patient exhibited a decrease in the size of the roentgen shadow of the heart a shift in the electrocardiographic axis from left to none at all and resorption of retinal hemorrhages and fluffy white areas of degeneration as well as clearing of blurred optic disk margins In another patient there was a moderate decrease in the transverse diameter of the heart In a third patient blurred optic disk margins cleared In one patient the electrocardiographic axis changed from left to none at all and the heart decreased in size following operation even though there was no reduction of arterial pressure levels This apparent improvement lasted about two years

Essential Hypertension Concept of Its Mechanism Arterial hypertension according to Henry A Schroeder[4] (Rockefeller Inst) is a state characterized by increased peripheral resistance owing to the presence of circulating pressor substances in the blood These substances are released by ischemic kidneys and may be of several varieties They cause changes in arterioles and in the hemodynamics of the kidneys leading to arteriolar affections A vicious circle is therefore established renal ischemia giving rise to hypertension which results in renal arteriolar sclerosis and the maintenance of ischemia (and hypertension)

Two conditions which occasion renal ischemia initiate this vicious circle (1) functional (spasmodic) constriction of arterioles by nervous or hormonal influences and (2) structural (organic) changes in the renal blood vessels A third condition renal arteriolar sclerosis arises as a result of hypertension and acts in such a way as

(4) Am J M Sc. 204 734 743 No mbe

to continue the existence of renal ischemia The first condition is probably active in most cases of hyper tension varying considerably in degree in different in dividuals but is capable of initiating it alone under the proper circumstances When organic renal ischemia is already present hypertension may result from slight intermittent increase in renal vasoconstrictor tone When the kidneys are otherwise normal the activity of the sympathetic nerves must be comparatively greater and their action called into play repeatedly to initiate the sequence of events leading to chronic hypertension

Arterial Hypertension Roy W Scott (Cleveland) reviews the evidence presented by Goldblatt and others which has established the renal origin of hypertension In essence the concept arising therefrom is that per sistent arterial hypertension is due to the resistance im posed by widespread hypertonicity of the peripheral arterioles which is excited by a renal humoral mechan ism Some however do not accept the validity of this concept If as they assume the kidneys are not con cerned in the pathogenesis of so called essential hyper tension then it would be reasonable to assume that most cases would show no significant renal disease But as is well known they do show renal disease and many com petent observers claim that they have never seen a case of prolonged hypertension in which careful necropsy did not reveal diseased kidneys Thus Bell and Clawson in a careful study of 420 cases of essential hypertension found renal arterial disease within the kidney paren chyma in 97 4 per cent and sclerosis of the afferent glo merular arterioles in 89 4 per cent Fishberg reported renal arteriolar sclerosis in 100 per cent of 72 cases of essential hypertension

The fact that protracted hypertension occurs without demonstrable renal excretory insufficiency afforded the major support for the concept of essential or nonrenal hypertension Now that the experiments of Goldblatt and others have demonstrated the role of the kidney in

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generation of the sympathetic innervation of the lower extremities as indicated by sweating and skin resistance tests and skin temperature studies

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(4) Am J M Sc 04 734 743 N mber 194

regarded as a psychic pressor test and has been recognized as having essentially the same significance

The extreme variability in the blood pressure level systolic as well as diastolic dictates reserve in drawing conclusions from casual blood pressure readings The variability of the blood pressure when studied by frequent determinations throughout the day and its lability under the influence of certain drugs have been used as a prognostic guide and an index of the suitability of various therapeutic procedures In the initial stages of hypertension there is a decided variability of hypertension but as the initial variable arteriolar spasticity is gradually succeeded by organic changes in the arterioles in the form of hypertrophy of the media and arteriolar sclerosis arteriolar relaxation becomes less frequent and less complete and the level of the blood pressure tends to become fixed at higher levels Diurnal variation becomes less pronounced and there is only an incomplete fall in blood pressure toward normal during sleep or after intravenous injection of barbiturates which remove the tonic sympathetic influence and indicate the degree of residual arteriolar spasticity

The level of the blood pressure and its lability is of undoubted value in interpreting the degree of hypertension and extent of the arteriolar changes but it does not give accurate information concerning the duration of the hypertension and the equally important atherosclerotic changes which are largely responsible for mortality in hypertension Mortality from heart failure and degenerative vascular changes resulting from long standing hypertension occurs without any necessary relation to its degree The limitations of blood pressure levels and tests of reactivity which measure the degree of hypertension and its effect on the arterioles are therefore evident

Two changes occur regularly with increasing duration of hypertension which can be evaluated objectively and which are useful as prognostic guides These are left ventricular hypertrophy and eventually atherosclerotic

producing hypertension that pronounced and persistent elevations in blood pressure may be produced in animals which exhibit no demonstrable evidence of renal excretory insufficiency those who still adhere to the non renal concept of hypertension are deprived of their most cherished argument The hypertension in animals with the main renal arteries constricted but without manifest renal excretory functional disease is, as far as concerns the phenomenon of hypertension the experimental counterpart of benign essential hypertension observed in man Even the clinical picture of malignant hypertension has been produced in the hypertensive animal by further narrowing of the renal arteries Such animals exhibit the changes observed in human malignant hypertension i e papilledema retinitis and protein retention with uremic death and at autopsy show the same type of arteriolar necrosis as that seen in man

Prognosis in Hypertension Robert M Daley, Harry E Ungerleider and Richard S Gubner[6] (Equitable Life Assurance Society of the U S) state that an important consideration in prognosis is proper evaluation of the duration of hypertension apart from its degree Since degenerative atherosclerotic changes may occur in the absence of advanced arteriolar disease it appears that the grading of hypertension solely by arteriolar changes which indicate the degree and not necessarily the duration of hypertension has certain shortcomings Duration is therefore emphasized as a prognostic guide Methods for evaluating the stage of the disease are considered

Subjects whose blood pressure rises to abnormal levels under any circumstances are predisposed to subsequent hypertension Several tests using various pressor stimuli have been devised to measure the reactivity of the blood pressure as an index of potential hypertension These tests must be used judiciously for while some are simple meticulous attention to details is required and a basal level must first be attained In effect the initial blood pressure reading on physical examination may be

(6) J A M A 1 1 383 389 Feb 6 1943

regarded as a psychic pressor test and has been recognized as having essentially the same significance

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Two changes occur regularly with increasing duration of hypertension which can be evaluated objectively and which are useful as prognostic guides These are left ventricular hypertrophy and eventually atherosclerotic

changes particularly in the coronary vessels and th aorta Both may be evaluated by roentgenography and *electrocardiography*

Blood Pressure as a Factor in Mortality is discussed by Karl W Anderson[7] (Minneapolis) Robinson and Brucer recently studied the blood pressure of 11 383 persons They found (1) that the normal range of systolic pressure for men and women in 90 120 mm Hg and (2) of diastolic pressure 60 80 mm Hg, also (3) that normal blood pressure does not rise with age but that prehypertensive and hypertensive blood pressures *do This study definitely refutes the concept that 100* plus the age is the normal or average blood pressure for adults

Average blood pressure is not the same as normal blood pressure Surveys indicate that normal blood pres sure is below the average pressure for each age group The most favorable mortality is found where the systolic pressure is below the average Evidence indicates that the most favorable point might be as low as 15 20 mm *below the average These findings brand as fallacious* the concept that hypotension in the absence of a pathologic process is detrimental to health Furthermore the favorable effect of low blood pressure increases with advancing age

Mortality rises in each age group with an increase of 5 mm Hg or more above the average blood pressure for the group Statistically 140/90 constitutes the ap proximate upper limit at which insurance may be issued without incurring risk of definitely increased mortality These figures however are above normal blood pressure

Blood Pressure in the Aged Henry I Russek[8] (Staten Island N Y) studied the blood pressure levels of 1 000 retired seamen aged 60 95 Age distribution was fairly uniform throughout The systolic pressure rose from 147 mm in the 60 64 year group to 160 mm in the 85 95 year group Pulse pressure increased from 65 to 74 mm

(7) Jo rn l La i 4 341 345 S ptember 1942
(8) Am Heart J 6 11 19 J ly 1943

over the same period The diastolic pressure varied only slightly in the men who were over 65 years of age

All blood pressures below 150/95 were classified as normal when the systolic and diastolic levels exceeded 150/95 diastolic hypertension was said to be present whereas systolic pressures above 150 mm with diastolic pressures under 95 mm were regarded as indicative of systolic hypertension The percentage of normals decreased from 67 per cent in the 60 64 year group to 34 per cent in the 85 95 year group Slightly less than half the 1 000 subjects had blood pressures of 150/95 or less The incidence of systolic hypertension rose progressively with age from 17 to 38 per cent and of the entire group more than one fourth had this type of blood pressure elevation On the other hand the incidence of diastolic hypertension seemed to rise more slowly with age (16 to 28 per cent) and those who manifested it comprised less than one fourth of the entire group Of the 1 000 subjects therefore approximately two in four were normals one in four had systolic hypertension and one in four had diastolic hypertension Actually however the commonest type of blood pressure elevation was systolic hypertension it was present in more than one third of all subjects over 75

An analysis was made of the variations in normal blood pressure with age In the 496 subjects in this class the average normal systolic pressure rose from 132 mm in the 60 69 year group to 136 mm in the 80 95 year group Others have stated that this rise is not the result of changes in normal pressure (120 mm or less) but shows that prehypertensive levels were included in the normal group Nevertheless in this study the incidence of normal pressure (in the restricted sense) decreased with age whereas the incidence of upper levels of normal showed a corresponding rise This suggests that among elderly persons all levels of normal systolic pressure tend to increase with advancing years In sharp contrast the average normal diastolic pressure decreased slightly with age and the incidence of low

diastolic pressures were found to increase concomitantly

A study of the ratio of actual to expected mortality revealed that the life expectancy of those with systolic hypertension was of the same order as for those with *normal pressure Diastolic hypertension on the other* hand carries a much more unfavorable prognosis For practical purposes the clinician may regard systolic hypertension in the aged as normal

Rationale of Medical Management of Patients with Arterial Hypertension is reviewed by Alfred W Harris[9] (Baylor Univ) Studies of Hines and of Robinson and Brucer show clearly that instead of the usually cited 150/95 or 140/95 zone as indicative of hypertension, normal pressures are more likely to be 90 120 systolic and 60 80 diastolic Robinson and Brucer particularly point out that a normal person attains his mature blood pressure at about adolescence and keeps that range throughout life It is now known that blood pressure does not rise with age but that prehypertensives and hypertensives do have such rises in blood pressure with age Furthermore *transient elevations of blood pressure* should not be ignored for they almost invariably indicate a more permanent rise in the future Persons with so called low blood pressure ' even at the range of 80 systolic have the lowest mortality rates

Anxiety often may be induced by blood pressure phobia and often is responsible for further accentuation of hypertension It is seldom necessary, except in rare cases of malignant hypertension, for a patient with uncomplicated hypertension to become an invalid Certainly mental unhappiness in such cases counterbalances any beneficial effects of physical rest Patients with uncomplicated hypertension tolerate moderate exercise well and react with the same qualitative physiologic response as normal individuals A patient should rearrange his life and learn to relax A mid day rest of one or two hours and regular sleeping habits are indicated Week ends spent in quiet *relaxation are recommended* espe

(9) Tr St te M J 14 7?7 2733 July 194?

cia'ly if some light sport or hobby occupies attention Vacations two or three times a year are desirable No special diet has proved valuable a balanced diet with normal salt rations is the one of choice Reduction of obesity is advisable Use of tobacco is not contraindicated in uncomplicated hypertension unless the patient shows hypersensitivity Bowels should be regulated and daily action without undue strain obtained Baths should be moderately warm and not below 34 C

The following drugs and procedures have been found wanting all the nitrates bismuth subnitrate the iodides benzyl benzoate theobromine and allied drugs atropine and the various belladonna derivatives (even those with sulfur) garlic akineton calcium salts mistletoe extracts various cholines organ extracts of liver pancreas ovaries and thyroid high frequency currents venesection lumbar puncture low protein diet and Allen s low salt regime

No review of therapy of essential hypertension should omit mention and adequate discussion of the thiocyanates Harris believes they are the only effective drugs now available but that they will one day be supplanted Thiocyanate may be given as either sodium salt or potassium salt Harris prefers Lilly s enseal of potassium thiocyanate 3 gr size It may also be given as a 5 per cent solution in various vehicles In this dilution usually used for ambulatory patients 4 cc is equivalent to 3 gr There is no necessity for hospitalization Harris routine is to give 3 gr doses three times daily for fiv days then twice daily for two days A blood level is then obtained and further dosage adjusted accordingly Optimum level at beginning is 8 12 mg per cent After four to six weeks in successful cases the usual maintenance dose will be 3 6 gr daily When optimal objective and subjective results have been maintained the lowest possible blood level consistent with maintenance of therapeutic effects is the goal After the original period of adjustment the patient can usually be seen once every three or four weeks for examination and

measurement of blood concentration Thiocyanate should be restricted to patients under 60 with uncomplicated arterial hypertension No patient with obvious arteriosclerotic changes, with a history of renal failure angina pectoris or congestive heart failure or with known myocardial infarction or cerebral accident should be given the drug

In conclusion Harris quotes the late Soma Weiss To what extent will the careful management of patients with arterial hypertension alter their progress and longevity? In a small proportion of cases the blood pressure will return to normal and symptoms will disappear either permanently or for long periods Such remissions however may occur spontaneously In a second group there will be some lowering of the blood pressure although not to normal level with accompanying subjective improvement and some checking of the disease A third and unfortunately larger group of patients will show no material lowering of the pressure but their symptoms will be lessened and they will be able to live more comfortable lives Accordingly acute cardiovascular accidents may be averted and to that extent lives will be prolonged The remainder will unfortunately progress inexorably to a fatal termination It is our hope that the specific antagonist or inhibitor of the vasoconstriction will be found in the near future so that more of these cases will fall into group I Renal extract studies have been far from conclusive

Why Are So Many Preparations Said to Reduce Blood Pressure in Cases of Hypertension? E V Allen[1] and other investigators have shown repeatedly that blood pressure is not static in hypertension but widely fluctuant A patient presenting a blood pressure of 240/130 mm Hg when seen initially may show a drop to 150/100 mm Hg during the first day of hospitalization if blood pressure is determined frequently Lesser fluctuations are common Such wide variations are probably responsible for the alleged hypotensive effect of

(1) Proc Staff Meet Mayo Cl 17 519 5 0 Oct 7 194

many preparations Also contributory to such fallacy is the tendency to report the highest figure observed before treatment and the lowest figure for blood pressure observed after treatment

The placebo effects of treatment of any kind are not so obvious as the spontaneous fluctuations in blood pressure In most hypertensives nervous strain and anxiety increase blood pressure Repeated conferences with a physician reassurance and knowledge that the high blood pressure is being treated will reduce blood pressure of many hypertensives Such an effect should not be confused with the effect of a specific remedy

Certain criteria should be fulfilled before the hypotensive effect of any procedure can be affirmed Blood pressure must be determined repeatedly before treatment is begun e g two or three times daily for one week and charted to aid quick comprehension Treatment may then be begun and after an appropriate time the studies of blood pressure should be repeated If there is no reduction in blood pressure treatment may be considered valueless If reduction results treatment should be discontinued If blood pressure then remains at a low level despite withdrawal of medication no specific effect of medication can be accepted If blood pressure returns to pretreatment values substitution of a placebo for medicament is advisable

Allen believes that such a plan would disclose that many remedies have either no effect or a nonspecific effect

Blood Pressure and Sulfocyanates (Thiocyanate) Sulfocyanates are naturally present in the body in a much higher concentration than any other known depressor substance The natural blood concentration of sulfocyanates is approximately 50 000 times that of nitrites Verne S Caviness Thomas L Umphlet and Chauncey L Royster (Raleigh N C) found the natural concentration of blood sulfocyanates in 241 persons to range from 0 31 to 2 55 mg per 100 cc blood

(2) Am J M S 04 688 697 N mb 194

In individuals whose pressure was in the normal range the concentration averaged 1 2 mg per 100 cc blood These levels tend to be constant for a given individual and to vary inversely with the blood pressure level whether naturally or under treatment Thus there is a definite tendency for low blood sulfocyanate levels to be associated with hypertension while high concentrations are not

These findings place the use of sulfocyanates in hyper tension on a rational basis The essential factor in treat ment of hypertension is to furnish a sufficient amount of sulfocyanate to balance an unknown amount of pressor substance and maintain blood pressure at a satis factory level This level must depend on the degree of change in arterioles and capillaries the cardiac reserve and pressor substances

The earlier in the disease treatment is instituted the better are the results that can be anticipated The potas sium salt appears to be the form best suited for sul focyanate therapy It is not toxic in therapeutic doses and is given in larger doses than the sodium salt As an initial dose 5 gr is given daily preferably after break fast

This drug shows no tendency to the development of tolerance to its action However there is a cumulative ef fect in many cases this makes frequent determinations of the blood concentration necessary It is noteworthy that as the blood concentration of potassium sulfocyanate rises, blood pressure falls At the beginning of its ad ministration weekly blood tests appear to be adequate Later, as the patient s response to the drug is better known tests are made less frequently and still later at monthly intervals Best results have been found to fol low the lowest effective blood sulfocyanate concentration Many patients do best with a concentration of potassium sulfocyanate of 2 5 to 3 mg per 100 cc blood this is within or near natural levels found without sulfocyanate therapy Others require a concentration of 5 to 8 mg or more per 100 cc blood The lowest concentration that

yields results should be used No maximum concentration has been set though 20 mg per 100 cc blood is usually accepted as a high safe range The authors have observed concentrations of 40 and 65 mg per 100 cc blood without serious ill effects However it appears that death may be produced at lower levels To avoid untoward symptoms pressures must be reduced slowly and gradually The effects of sulfocyanates develop slowly and persist for a considerable time after therapy has been stopped Frequently it is necessary to reduce the dose Occasionally after several weeks it is necessary to increase the dose above 5 gr daily The authors have observed that with improvement in blood pressure and symptoms dosage may be reduced gradually after weeks or months of treatment

Fatal Poisoning from Potassium Thiocyanate Treatment of Hypertension was observed in a case reported by William O Russell and William C Stahl[3] (Washington Univ) Death resulted from ingestion of 5 6 Gm potassium thiocyanate given in 6 gr daily doses for 14 days This is less than the amount usually prescribed for treatment of hypertension Five similar cases have been collected from the literature In all the cases a definite clinical syndrome developed characterized by profound weakness and a toxic psychosis with delirium hallucinations mental confusion and convulsive movements The maximal amount of thiocyanate administered in any one case was 14 4 Gm over 18 days The highest blood concentration of cyanate occurred in the authors case being 21 7 mg per 100 cc blood Necropsy in three cases disclosed no characteristic pathologic change that could be attributed to thiocyanate intoxication

Role of Surgery in Management of Patients with High Blood Pressure Thomas Findley[4] (New Orleans) believes that lumbodorsal splanchnicectomy as devised by Smithwick is the operation of choice for essential hypertension because it affords more complete denerva

(3) J A M A 119 1177 1181 Aug 8 194
(4) T i St t M J 15 2799 80 O t b 194

tion of the splanchnic bed and lower extremities Best results are obtained in young subjects with symptoms associated with wide spontaneous fluctuations of blood pressure The operation should be done early, but it is difficult to persuade patients to submit to it until they have passed the stage where maximal benefit will accrue Sympathectomy is not the answer to essential hypertension but it is the only available treatment which has produced apparent cures and prolonged life expectancy Even though it may fail to reduce blood pressure, it will almost certainly afford worthwhile relief of symptoms in a high percentage of cases It entails almost no operative mortality It should be done early or not at all

[Paul White although skeptical for a number of years as to its efficacy tells me he has become quite enthusiastic over the recent results of Smithwick s operation.—Ed]

Surgical Treatment of Hypertension Results in 54 cases reported by Elmer C Bartels James L Poppen and Robert L Richards[5] (Boston) confirm the experiences of others namely that surgery of the sympathetic nervous system may have an ameliorating effect on the blood pressure of patients with essential hypertension Best results were obtained in patients with moderate or moderate to severe hypertension whose ages were less than 40 and whose blood pressures responded to sedation Among 38 carefully selected patients 13 had an excellent result and 11 a slight drop in pressure The blood pressure of the remaining patients was not altered Symptomatic improvement occurred in 71 per cent of the patients in one half of these the blood pressure remained elevated Careful selection of patients for this operative procedure is emphasized

HYPOTENSION

Arterial Hypotension Thomas M Durant[6] (Philadelphia) analyzes recent evidence indicating that arterial hypotension is not a disease entity and presents thera

(5) Ann Int Med 17 807 811 No mb r 194
(6) Pen syl n a M J 45 1185 1191 A g t, 194

peutic implications which can logically be derived therefrom Postural hypotension is also discussed

Essential Hypotension—There is no general agreement as to what should be considered a lower norm of blood pressure the most commonly accepted has been 110/70 mm Hg but surveys of large groups have shown systolic pressure below 110 in 25 per cent and diastolic below 70 in 34 per cent This however does not prove that hypotension is not a disease entity therefore statistics on mortality and morbidity of this group were reviewed These disclose that expected mortality is definitely lower in the hypotensive group than it is in either the hypertensive or the normal blood pressure group But despite longevity of the hypotensive group symptoms and disability might still result from such hypotension and were this the case hypotension might still warrant designation as a disease entity The relationship of low blood pressure must therefore be considered

Symptoms most frequently attributed to hypotension are lassitude dizziness headache lack of stamina nervousness and cold extremities Yet all persons with hypotension do not have these complaints and many are robust The person with symptomatic hypotension however is notable because of his habitus and general condition Characteristically he is of linear build is underweight affects sedentary habits and takes little exercise Nervous instability is frequent and the body temperature tends to be subnormal This presents the problem of whether symptomatology is due to hypotension or whether both symptomatology and hypotension are due to habitus and physical condition

Evidence derived from clinical studies is pertinent First it is possible to obtain complete alleviation of symptoms in most cases of this type by graduated exercises and dietary measures to correct the weight deficiency The remarkable feature about the alleviation thus obtained is that the symptoms disappear even though blood pressure remains unaltered Furthermore drugs which elevate blood pressure without psychic

stimulation do not completely ameliorate symptoms even when pressure is raised thereby to average levels This suggests that hypotension is not the primary factor in the symptomatology but is a symptom in itself a manifestation of subnormal body tonus

Postural (Orthostatic) Hypotension—Adequate comprehension of postural hypotension necessitates consideration of the circulatory adjustments which occur in the normal individual with a change from recumbency to standing These are (1) the neurogenic peripheral vasoconstriction which acting throughout all the dependent portions of the body, tends to prevent pooling of blood in these portions (2) reflex acceleration of the heart rate and (3) muscle tonus These adaptive mechanisms do not tend to remain equally effective under all conditions This is well illustrated by the frequency of syncope among standing spectators *on hot days* These mechanisms are also more effective toward evening than in the morning Also influential and thereby contributory to production of orthostatic hypotension are nervous fatigue postinfectional convalescent states pregnancy and neural pathology

The patient with postural hypotension complains of attacks of syncope dizziness or dimness of vision *The* significant finding is a marked drop in blood pressure which occurs when the patient assumes the standing position or when he has been standing quietly for several minutes some present associated tachycardia Fluoroscopy with the patient upright will disclose a small droplet type heart Electrocardiograms taken with the patient standing often reveal inverted T waves in leads II and III These revert to normal with recumbency In diagnosis neurologic disease such as tabes dorsalis and multiple sclerosis should be ruled out

Therapeutic agents are the vasoconstrictors *ephedrine amphetamine* and paredrine Ephedrine sulfate $\frac{3}{8}$ $\frac{3}{4}$ gr *thrice daily*, often alleviates symptoms but may have disagreeable side effects Amphetamine *sulfate* usually given in *10 to 20 mg* dosage on arising and again at

noon is often effective and has no side effects Paredrine hydrobromide has an advantage over amphetamine in that its action is seemingly confined to the peripheral sympathetic mechanisms Lacking the cerebral stimulation of amphetamine it does not cause insomnia if given late in the day It may be prescribed in 20 mg doses every two hours during the day or may be used to supplement the two dose amphetamine schedule

Nonmedicinal measures include dietary regulation graduated exercises avoidance of long periods of standing immobile abdominal supports and sleeping with the head of the bed elevated 18 in

Psychoneurosis

Anxiety and the Heart According to Edward Weiss[7] (Temple Univ) there exists an actual relation of anxiety and anxiety attack to disorders of the heart and cardiovascular system Anxiety neurosis is closely related to physiologic changes particularly with regard to the cardiovascular system Moreover in its varying degrees it is probably the most frequent disorder of civilized life Freud long ago described the various forms of anxiety attack Not only did he call attention to disturbances of cardiac function such as palpitation arrhythmia and tachycardia but he also described disturbances of respiration and other physiologic changes which today are often regarded as evidences of vasomotor instability or autonomic imbalance He emphasized that these attacks are not always accompanied by *recognizable anxiety*

Cardiac neurosis arises in predisposed persons subjected to a precipitating factor Such persons carry an unusual amount of anxiety in their make up Under special circumstances that anxiety is attached to the heart largely because it is regarded as the all important organ of the body and is associated with the idea of sudden death [It seems a shame that newspapers fill their obituary columns with announcements of death

7 J A M A 1 916 931 Dec 194

from heart disease and never mention the cause of death in cases of cancer or tuberculosis —Ed] The anxiety or even the personality predisposition may not be obvious but careful inquiry in such cases will frequently elicit a story of nervous breakdown during some stress period The most frequent precipitating factors are (1) statement of some physician or life insurance examiner that the heart shows some abnormality such as a murmur or arrhythmia (2) occurrence of some dramatic case of heart disease among relatives or friends (3) appearance of some symptom which calls the patient s attention to his heart and leads to doubt as to its integrity (4) some profound and protracted emotional disturbance in which however there is at first no element of doubt concerning the state of the heart The last is frequent among cases of irritable heart in soldiers effort syndrome and neurocirculatory asthenia

Under these circumstances pain in the heart region fatigue sighing respirations insomnia ringing or pounding in the ears and faintness dizziness nervousness irritability and flushes are apt to appear At first there may be only discomfort in the heart region with later development of other symptoms particularly fatigue which may be overwhelming and lead to complete invalidism

The chief symptoms may be grouped as follows (1) pain and distress in the heart region (2) dyspnea and fatigue (3) palpitation or heart consciousness, (4) tachycardia and other disturbances of rhythm (5) a group of symptoms which include all of the foregoing in addition to evidences of vasomotor instability, usually classified as neurocirculatory asthenia Pain in the heart region requires careful evaluation to distinguish the anginal syndrome from the many other conditions which may simulate it Dyspnea is the most common symptom of heart disease but cardiac dyspnea is in the main a reflex rather than a chemical disturbance and its most important cause is pulmonary congestion Heart consciousness which comprises eit ar

dia or arrhythmia or both is a frequent symptom in the cardiac neuroses and often leads to erroneous diag nosis But emotion may also slow the heart and occasionally during anxiety attacks especially in night mares great slowing apparently from vagal stimula tion occurs More frequently however the heart is accelerated and this together with premature contrac tions may lead to heart consciousness

Murmurs are the most frequent cause of false diag nosis of cardiac disease A systolic murmur can be found in a large number of healthy young adults if they are examined in various postures in different phases of respiration and before and after exercise These functional murmurs are also much more common during fevers They are rather faint but sometimes moderately loud and are heard in the apical or pul monary areas Kilgore feels that if they are not very loud not high pitched and not accompanied by other signs of heart disease deficient heart function or a history of rheumatism or chorea and are markedly changed by respiration and posture these systolic mur murs should not be regarded as pathologic In the case of borderline systolic murmurs—some of the louder ones less clearly dependent on posture or respiration—the diagnosis of valvular disease if suspected but not confirmed by other physical signs should in general be withheld until roentgenographic and electrocardio graphic studies have been made

The first point in the prophylaxis of cardiac neurosis enters in regard to this problem If there is any ques tion regarding the significance of the murmur the pa tient had better not be apprised of the fact or even made suspicious of heart disease until further evidence is obtained This is of special significance in recruit ment

When examining patients predisposed because of their neurotic personality structure the physician must be particularly careful not to focus attention on the heart during a general physical examination particu

larly when this is conducted during an anxiety attack He must definitely state that the patient does not have heart disease rather than to say that he does not think the patient has heart disease If medicines are used during the anxiety state the patient must have definite understanding that they are palliative rather than curative and that they have nothing to do with the

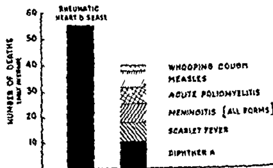


Fig 58 —Rheumatic heart disease caused more deaths between ages of 5 and 29 than six other diseases combined from 1935 to 1939 (Spekter below)

heart itself Thus if small doses of sedatives are used it is wise to explain to the patient that they will relieve his nervousness Use of digitalis is, of course a blunder

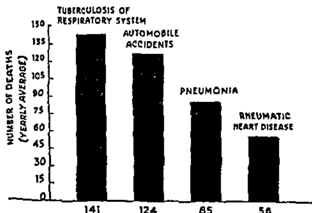
In most of these cases the physician will be able by tactful questioning to unearth the reason for the anxiety state In some of course such analysis must be made by a psychiatrist

Rheumatic Fever

Rheumatic Fever in the United States Its Public Health Implications *Louis Spekter*[8] (Connecticut State Dept of Health) compares the death rates of rheumatic heart disease with those of other infectious diseases to show the relative numerical importance of rheumatic fever In Philadelphia (1936), if all ages are taken together, rheumatic heart disease is exceeded as a cause

(8) Connecticut M J 7 156 163 March 1943

of death only by tuberculosis lobar pneumonia and syphilis It ranks third as a chronic infectious disease exceeded only by tuberculosis and syphilis It caused more deaths in persons under 20 years than pulmonary tuberculosis and more than pertussis measles meningococcic meningitis diphtheria scarlet fever and poliomyelitis combined In Connecticut the rheumatic fever



F g 59 —C mp n of d th b tw n ges of and 9 d to heum t h art dises w th th of th m t mp rt t c us f de th f om 1935 to 1939

mortality compares similarly with these other diseases (Figs 58 and 59)

The mortality from heart disease in New York City (1933 1936) was greater than that from all other causes of death among girls of 5 14 while among boys it was exceeded only by accidents

Thus existing data indicate that the prevalence of rheumatic fever in the United States is of such magnitude both relative and absolute, as to constitute an important public health problem

[Rheumatic fever is certainly a far greater public health problem than infantile paralysis and yet in comparison the funds expended for its prevention and treatment are insignificant.—Ed.]

State Programs for Care of Children with Rheumatic

Fever under the Social Security Act[9] are reviewed At present 14 states have programs in operation for care of children with rheumatic fever or heart disease About five other states intend to submit plans for rheumatic fever programs during the fiscal year 1943, and at least 10 additional states have informed the Children s Bureau of their serious interest in such a program It will be impossible for every state in the Union to receive additional federal funds for provision of services to children with rheumatic fever until further funds are made available through amendment of the Social Security Act

In about half the state programs children are given sanatorial care during the chronic phase of rheumatic fever at convalescent homes where medical, nursing and social supervision are adequate for the care of the sick child in bed Convalescent homes are also being used for children who have entirely recovered from rheumatic fever but who are not physically up to par because of the recent attack of rheumatic fever or some other illness

The convalescent homes which are being used in state rheumatic fever programs meet the standards set up by the Children s Bureau advisory committee in regard to medical nursing social and nutritional supervision isolation facilities adequate records and provision for recreation

Preventive and Public Health Aspects of Rheumatic Fever in Children are discussed by Louise Fry Galvin[1] (Richmond) Although the specific causal agent of rheumatic fever has not yet been determined many facts which aid in control of the disease are known Thus there is a strong familial tendency toward the disease 8 10 per cent of exposed persons in rheumatic families acquire it as compared with 3 per cent in control families A hereditary factor may also be active Initial attacks occur most commonly between 4 and 15 years and are

(9) Child en s Bure u U S D p tme t f Iabo 1943
(1) S uth M J 36 116 121 F b ry 1943

rarely seen before 2 years or after 20 The highest incidence of attacks is in late winter and early spring and damp cold climates predispose toward the disease

A close relationship between rheumatic fever and the streptococcus is also recognized With regard to this it may be questioned whether this is due to the fact that the rheumatic patient is particularly susceptible to streptococcic infections or whether the streptococcus activates some other condition latent in the host or whether rheumatic fever represents some peculiar immunologic response to streptococcic infections

From the standpoint of public health and prevention the most significant factors in causation of rheumatic fever are social and economic in nature They include damp congested living quarters malnutrition lack of sunshine inferior medical care and inadequate clothing

The program of prevention must cover many phases These include prevention of the disease itself prevention of heart damage once the disease has occurred prevention of recurrences and prevention of mental and emotional maladjustment in the patient and in members of his family Educational and case finding campaigns are therefore essential Hospital and convalescent care must be provided Hospitals are best for the child in the acute stage but during the long period of convalescence a convalescent home is best These should be especially organized for the purpose with children *divided into small units and carefully guarded* against upper respiratory tract infections Children so cared for are spared the effects of emotional and mental strain which commonly develops in families caring for a chronically ill individual In the convalescent home with well directed group care children respond unusually well and cheerfully to routine and instruction They can keep up with their school work be taught occupational therapy group play and co operation and be *given proper insight into themselves* and their condition Also careful medical and nursing su

pervision can be given with a minimum of effort and expense However when a child is separated from the family group for a long period, it is necessary through nursing and social service agencies to educate the family as to the proper future care of the child to improve the home and keep it receptive to the child's reentrance

Possible Methods for Prevention of Rheumatic Manifestations in the Armed Forces are discussed by Ronald Hare (Univ of Toronto) While the exact cause of acute rheumatism is not yet known, it is probable that two primary conditions must be fulfilled before the disease can develop There shall have been a streptococcic infection and also some as yet unrecognized factor in the environment, for some localities and social strata are more susceptible than others Other than general measures therefore the best method of preventing rheumatic disease is to prevent streptococcic infection

In addition to bacteriologic control measures such as identification and isolation of carriers, proper management of barrack rooms constitutes a significant part in control of streptococcic infections Studies have shown that bed making and sweeping of these rooms is the best possible way to disseminate infection for at the time when these procedures are carried out the droplets containing the streptococci have dried and the organisms are readily spread in the dust which is raised Accordingly it is recommended that the beds be merely straightened and only dismantled occasionally When this is done the windows should be wide open to disseminate the infected particles as quickly as possible The barrack rooms should be swept when the men are out and a sweeping compound of some type should be used to lay the dust The beds should be spaced as widely as possible Use of double tiered bunks is unsound for droplets expelled by an individual in the upper tier would tend to fall by gravity and infect the individual occupying the lower

(2) Canad M A J 48 116 1?1 February

U e of ultraviolet light aerosols and propylene glycol vapor and oiling the blankets have been suggested as suitable methods for cutting down cross infection These methods may be of value but suitable technics have not yet been worked out which would permit their application to service use

Nature of the Rheumatic Child According to Douglas Hubble[3] less than 10 per cent of children entering the rheumatic state do so by way of subacute rheumatism and such children more often show evidence of continued nervous instability than of infection More than 25 per cent of children becoming rheumatic do so by way of chorea and it is suggested that this condition also is evidence not of infection but of profound nervous instability Hubble concludes that nervous instability is a factor of considerable importance in development of the rheumatic state and accordingly suggests that treatment should include simple psychotherapy and sedation to remove growing pains reduce relapses in chorea and improve mental and physical performance

Rheumatic Heart Disease A Phase of Rheumatic Fever Chester S Keefer[4] (Boston Univ) divides patients with rheumatic fever and rheumatic heart disease into three major groups on the basis of outcome The first includes patients who die of acute carditis Deaths among all patients with rheumatic fever within the first year will vary between 2 and 5 per cent but among patients who show acute carditis as the initial feature the rate may be 15 20 per cent The second group comprises patients who have repeated attacks of clinical rheumatic fever with cardiac damage These patients may do one of several things (1) die during an attack of acute carditis or (2) pass into a latent phase and then develop bacterial endocarditis heart failure from valvular disease with or without recurrent active infection heart failure with auricular fibrillation or heart failure with embolism The third group

(3) B it M J 1 154 158 F b 6 1943
(4) T [illegible] t Cl 1 117 144 M h 194

consists of the 15 25 per cent of patients with rheumatic fever who recover completely without any signs of heart disease As a rule these patients have a single mild attack without signs of acute carditis, and recovery is obvious within the first year Whether a patient recovers completely would seem to be related to (1) age of onset (2) severity and duration of attack and (3) type of manifestation Thus it would appear that acute rheumatic fever tends to be less severe in adults and in those with a mild single attack or polyarthritis or chorea On the other hand patients who have signs of acute carditis severe chorea or polyarthritis and who are under 12 develop heart disease most often Generally if complete recovery occurs it takes place within the first year after an attack and all signs disappear

Observations on Diagnosis and Treatment of Rheumatic Heart Disease J D Keith[5] (Toronto) states that in many cases of rheumatic disease diagnosis is not difficult However there are cases in which the history and findings are not so clearcut To distinguish between rheumatic and nonrheumatic pains it is helpful to ask the child to point to the site of the pains If he points to a joint the pain is more apt to be rheumatic than if the muscles are involved Swelling or local heat in the joints adds weight to the diagnosis Rheumatic pains are more apt to occur when the limb is first used in the morning or after playing in the cold and tend to disappear when the child is in a warm bed Pains that have been present for a year or two without other signs of rheumatism having developed are usually not rheumatic In the presence of joint pains elevation of the sedimentation rate is suggestive of a rheumatic process

Mild cases of chorea are sometimes difficult to distinguish from habit spasm Choreic movements are writhing and purposeless habit spasms are short spasmodic and exaggerated Choreic movements may interfere with eating writing or speaking and the res

(5) Practitioner 151 38 42 July 1943

piratory effort may be irregular and incoordinate In habit spasm there is often a history of mental conflict or emotional strain

The most important diagnostic difficulty is interpretation of heart murmurs Diastolic mitral or aortic murmurs are almost invariably rheumatic in children Diagnosis most frequently depends on finding the characteristic mitral systolic murmur however It is soft and blowing early in the disease and becomes louder harsher and more readily propagated later It is transmitted toward the axilla and the first heart sound may be obscured or absent

Prophylaxis is of major importance The danger period is in the five years following appearance of rheumatism If heart disease is not present at the end of that interval or if the heart is improved or even if it is no worse the outlook is usually good Frequent examination should be made Use of sulfanilamide in small doses as a prophylactic against recurrence is still experimental but shows promise The following measures should be applied as completely as possible both to the children who have had rheumatic fever or chorea but show no heart disease and to those who have developed cardiac disease (1) An optimal diet is important because rheumatic disease tends to affect mainly those with poor diets (2) Dental caries and alveolar abscesses should be corrected Tonsils and adenoids should be removed in most cases because sore throats are then less frequent (3) If a cold or sore throat develops the patient should remain in bed until all signs have disappeared (4) Adequate rest is most important Early to bed and a half hour rest at noon are helpful Varying degrees of restriction of exercise should be carefully chosen to fit the individual

The chief therapeutic measure during an acute attack is rest in bed particularly in a hospital equipped to give prolonged care until all signs of activity have subsided Salicylates are given to relieve joint symptoms and reduce temperature This helps control the

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(5) P a t t oner 151 38-42 J ly 1943

diac stimulants are used when indicated Digitaliza tion diuretics oxygen therapy and intravenous ther apy are used in heart failure Creation of a proper attitude toward the disease in the mind of the child and his rapid and correct adaptation to sanatorial care are of utmost importance An attempt is made to learn quickly the individuality of each child and to adjust professional care accordingly During rounds all pa tients are examined in a like manner irrespective of the medical status and progress notes are dictated within the hearing of the patients unfavorable com ment being omitted until after the rounds

All children receive bedside teaching individualized on the basis of limitations imposed on their abilities by the severity of the active infection Competitive exam inations and grading are avoided Occupational ther apy during the active period is not encouraged A child with symptoms of active disease or cardiac disability which are obvious to other patients is treated in a pri vate room When all clinical signs of activity have sub sided he enters the subacute stage and is removed to the convalescent building where a program leading to a rapid resumption of normal childhood activities is instituted

After the child has been observed in the convalescent building for several weeks he is transferred to an in active building if he shows no signs of rheumatic re activity and continues to show definite improvement nutritionally Here he is classified according to age group rather than to the extent of cardiac damage His daily activity approaches normal except for a two hour rest period after lunch and the omission of competitive physical exercises During the 8 to 10 months observa tion in the inactive building an attempt is made to bring about an early transition from sanatorium to home care No group instruction of parents is given but individual instruction is given in most instances with a view of presenting the problem of rheumatic heart disease in its proper perspective

pulse and so rests the heart Digitalis is of most use when chronic failure occurs In the acutely ill child with enlarging liver and little edema the drug should be given with great care since toxic symptoms such as missed beats or even auricular fibrillation more readily appear When the patient finally gets up it is wise to start with five minutes the first day and increase by only five minutes a day until he is up for about four hours

Sanatorium Method for Care of Rheumatic Heart Disease in Children Leo M Taran[6] (Brooklyn) describes the care of patients at the St Francis Sanatorium for Cardiac Children This institution consists of six buildings with 25 beds each Four buildings are devoted to ambulatory children recently recovered from a clinically active rheumatic episode one houses laboratories and one is devoted to children convalescing from a recent active episode who show only laboratory evidence of rheumatic infection

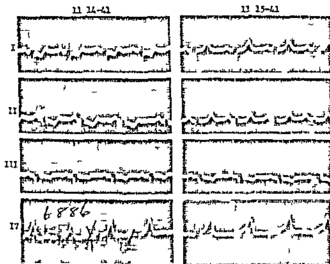
Any boy aged 6 8 and any girl aged 6 15 years with acute rheumatic fever is admitted Any form of rheumatic heart disease without regard to extent of anatomic lesion functional disturbance or cardiac size is accepted Completely inactive cases are not accepted The average stay at the sanatorium is 10 months Discharge is determined by the clinical course

On admission the condition of the patient is considered active until proved inactive Criteria for activity are (1) obvious signs or symptoms of active infection (2) secondary signs such as loss of weight pallor fever slightly elevated pulse rate rapid sedimentation rate etc (3) clinical impression of rheumatic carditis Complete bed rest is required until all criteria for activity have subsided

The medicinal armamentarium takes into consideration the fact that overtreatment delays recovery Medicinal therapy is at best only palliative and directed to alleviation of symptoms Salicylates sedatives and car

(6) J Pediat 3 69 78 July 1943

60) If the factor producing coronary insufficiency is slight or is exerted briefly there may be no myocardial changes If ischemia is prolonged and severe it may result in focal disseminated necrosis in the subendocardium and papillary muscles Location of the lesion explains the absence of pericarditis and mural thrombi



F g 60 —Man 54 w th o ary h rt d a te n ry ffi O dm n (N 14 1941) l t a d g m how d d p f RS T gm t n l d I d II w th m n f T w n th l d T a ng et d to rm l n N 15 1941

Coronary occlusion or thrombosis is a characteristic syndrome and presents specific electrocardiographic changes Occlusion is a better term than thrombosis since most occlusions are initiated by intimal hemorrhage and may form a complete arterial block without thrombosis The acute attack occurs irrespective of external factors such as effort and excitement but may be precipitated by operation and shock The pain of coronary occlusion is usually prolonged and is unaffected or aggravated by nitroglycerin Shock nausea and vomiting are common Blood pressure almost in

THROMBOSIS OF CORONARY ARTERIES

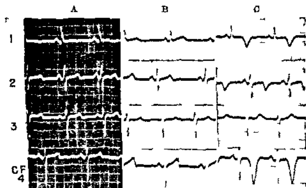
Coronary Insufficiency and Coronary Occlusion. There is still confusion about the meaning of the term coronary insufficiency and about the various forms of coronary heart disease which range from simple attacks of angina pectoris to complete arterial occlusion with definite *myocardial infarction* Most cases of coronary heart disease fall between these extremes. Arthur M Master H H Carroll and Cecil Andrews[7] attempt to clarify this middle zone

Angina pectoris due to coronary disease as distinguished from coronary insufficiency and coronary occlusion is a transitory attack of substernal or precordial pain precipitated by exertion emotion cold trauma, ingestion of food etc and relieved by nitroglycerin It is due to temporary ischemia and is not accompanied by any acute pathologic changes in the myocardium Shock vomiting changes in heart sounds heart failure and a drop in blood pressure are not present blood pressure may, in fact rise The electrocardiogram is unaltered or shows transient depression of the RS-T interval and inversion of the T wave

Acute coronary insufficiency is usually associated with a precipitating factor such as that seen in the ordinary attack of angina pectoris but may also be seen in tachycardia heart failure acute hemorrhage operation shock aortic stenosis or insufficiency and syphilis, which reduce the coronary flow or increase the work of the heart and oxygen requirement of the myocardium The clinical picture may resemble that of coronary occlusion but pain and signs of shock may be absent or inconspicuous Laboratory findings are minimal Electrocardiographically coronary insufficiency is characterized by depression of the RS T segment and T wave changes usually in two or more leads (Fig

(7) U S Nav M Bull 40 816 874 October 194

count was 10 000 sedimentation rate was elevated to 11 mm per minute The patient remained free of symptoms leukocytosis and fever for two weeks The electrocardiogram on admission showed slight inversion of T and upright T (Fig 61*A*) The pattern was thought to indicate left ventricular strain Five days later T had become upright (*B*) At the end of two weeks she was sent to the x ray department for a gastro intestinal series because of absence of clear indication of myocardial infarction and the previously mentioned relation of the pain to meals Following return from x ray study she had more pain the leukocyte count subsequently rose to 13 600 and the electrocardiogram showed deep in



F g 61—R d *A* s d bl l ft devi t l ght f T d p ght Ts, with l ghtly h gh g f ST t rp t d d t g l ft t ul st R d *B* fi d y l t h w l ght h ges in T w d bT gm t t d fl t ly t rm l R d (14 d fte dm h w m k d m p f T w in l ds I II nd IV

version of T T and T (*C*) There was gradual evolution of the electrocardiogram toward normal in several weeks She made good recovery but died of another myocardial infarction 1½ year later

It seems evident that this patient had coronary occlusion following a short period of angina pectoris but without definite evidence of myocardial infarction on admission The trip to the x ray department may have precipitated actual infarction by increasing metabolic demands at a time when the coronary blood flow could support resting needs only The possibility of a sudden unrelated occlusion cannot, of course be dismissed

Presence of prodromal symptoms probably depends

variably falls and distant heart sounds and gallop rhythm are frequent Occasionally a pericardial rub is present Heart failure often occurs and laboratory findings are always positive (fever leukocytosis and rapid sedimentation rate) There are usually residual symptoms for weeks or months The electrocardiogram shows typical, progressive changes consisting of RS T elevations and deep Q waves the former progress into T wave inversions There is usually a reciprocal relationship of the RS T segments and T waves in leads I and III This specific electrocardiographic pattern is associated with a confluent massive infarct extending from endocardium to pericardium and thus frequently giving rise to embolization and pericarditis Fluoroscopy often reveals systolic expansion in an area of the left ventricle

Premonitory Symptoms of Myocardial Infarction are discussed by Norman H Boyer[8] (Boston Univ) In a certain proportion of cases onset of myocardial infarction is not sudden and unpredictable but is preceded for a variable time by premonitory symptoms which should receive serious attention Prompt recognition and institution of measures designed to increase the absolute or relative coronary circulation may have favorable effects in some cases Seven illustrative cases are reviewed, one of which is presented here

Woman, 61, with hypertension for 12 years, had been well except for slight exertional dyspnea until two weeks before admission when she developed burning substernal pain on effort and after meals A week before pain increased in frequency and severity and even came on at rest on one occasion The day before admission she walked a mile and on the way home developed a severe substernal pain which gradually increased and radiated to the arms It lasted several hours, was only partially relieved by nitroglycerin and was accompanied by weakness and sweating On admission she had no pain or other complaints Blood pressure was 194/90 The heart was regular sounds were of fair quality, and there were no murmurs or gallop Lungs were clear and abdomen and extremities normal Temperature was normal Leukocyte

(8) New Engl nd J M d 7 6 8 633 Oct

or weeks an immediate increase although slight may conceivably keep all or part of the ischemic myocardium viable if such collateral flow is not hampered by reflex constriction of the vessels that provide the source for collateral circulation and if at the same time the metabolic needs of the heart are minimized Atropine may also be used although the tachycardia incident to its use may not be desirable

The Course of the Blood Pressure before during and after Coronary Occlusion was analyzed in 538 cases by Arthur M Masters Harry L Jaffe Simon Dack and Nathan Silver[9] (Mount Sinai Hosp New York City) The incidence of hypertension previous to the attack was probably over 70 per cent Slightly over half of the attacks were initial attacks and the remainder were second or third attacks

The blood pressure always fell during an attack Although the rapidity and degree of fall varied considerably it was possible to classify the blood pressure course during and after the attack into several types according to initial level degree and rapidity of fall and return toward the previous level and outcome of the attack In 57 per cent of the cases the fall was rapid i e in the first three days the blood pressure fell to a level approaching the lowest pressure during the attack In 42 5 per cent the fall was gradual reaching a low level in one to three weeks Occasionally a week or more elapsed before a significant fall became evident In most cases the lowest pressure was reached between the twelfth and the twentieth day The rapidity of the fall in blood pressure was influenced to some extent by the height of the pressure preceding onset of the attack A greater percentage of nonhypertensive patients showed a rapid fall than did those with hypertension The most rapid fall seemed to occur in nonhypertensives in whom the attack was fatal In the hypertensive group the incidence of rapid fall was the same in the fatal and nonfatal cases In general the trend of the blood pressure curves was

(9) Am H rt J 26 9 107 J ly 1943

on the rate at which the occlusive process in the coronary vessels develops Sudden complete closure of a large or moderate sized vessel will undoubtedly result in immediate infarction of the corresponding myocardium Atherosclerosis of the coronary arteries is progressive fortunately accompanied by production of collateral circulation when the need arises At times growth of collateral circulation is unable to keep pace with progress of the disease and when the disease is in ascendancy, symptoms appear or increase When symptoms are present indicating that the disease is progressing rapidly such as sudden increase of angina pectoris and onset of prolonged pain it seems reasonable to minimize metabolic demands of the heart by strict bed rest In all ischemic tissue there must be a peripheral zone in which the balance of supply and demand of blood is at a critical point A little more or less blood or demand may mean the difference between viability and death of the tissue Thus even if infarction occurs its size may in some instances be reduced by reduction in demands of the peripheral zone under conditions of absolute rest If the occlusive process develops slowly enough or if the affected area is small necrosis of the muscle may not occur There seems therefore little room for doubting the advisability of minimizing the demands on the heart when symptoms suggest that its blood supply is inadequate but whether or not tangible benefit accrues is difficult to evaluate

Emphasis has been placed on bed rest but other general measures should not be neglected chiefly sedation and avoidance of tobacco Cognizance should be taken of increase in cardiac work incident to large heavy meals and the diet should be arranged around light foods in small amounts Alleged coronary dilators are of secondary value The stimulating effect of the xanthines may be undesirable Papaverine may be used for its possible effect on overcoming spasm in unaffected vessels that supply the collateral circulation Although maximal collateral flow occurs only aft several days

infarction must always be considered particularly in elderly persons with sudden changes in the state of well being The sudden development of the usual symptoms of congestive heart failure should always suggest infarction other cardiac manifestations of atypical infarction include left heart failure and sudden changes in cardiac rhythm

The cerebral signs of cardiac infarction are of great interest It is well known that cerebral embolism is a common complication of infarction but this condition develops as late as the second week. It is not generally recognized however that cerebral manifestations may occur at onset of infarction and probably result from acute cerebral changes produced by inadequate blood flow The cerebral manifestations of cardiac infarction may be listed as follows (1) weakness faintness collapse or coma obvious results of a sudden drop in blood pressure (2) vertigo nausea and vomiting (3) psychic disturbances (4) hypertensive syndrome with headache vertigo etc (5) focal manifestations such as the sudden development of monoplegia or hemiplegia from transient ischemia thrombosis or later embolism

Certain Medicolegal Aspects of Coronary Thrombosis are discussed by F A Willius The question of the relationship of accidents to occurrence of coronary thrombosis is assuming great importance as the result of (1) increasing incidence of coronary thrombosis and (2) establishment of certain questionable legal precedents An impartial consideration of the facts in the case in respect to all phases of scientific knowledge has for its initial premise the knowledge that coronary thrombosis does not occur when the coronary arteries are normal Thus occurrence of coronary thrombosis must presuppose existence of coronary arteriosclerosis, and undeniable evidence based on correlation of clinical signs and necropsy findings attests to this fact

It cannot be denied that arteriosclerosis varying in degree and situation is a universal concomitant factor

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similar in the hypertensive and nonhypertensive groups but the absolute fall in pressure was greater in the hypertensive group The systolic blood pressure rarely fell below 90 mm in the hypertensive group but this was common in the nonhypertensive group When the pressure fell below 80 the patient usually *died* In almost one fifth of patients with a previous pressure of 200 mm. or more the pressure did not fall below 150 mm Two thirds of the hypertensive patients regained a hypertensive level in half of these this took place before discharge from the hospital and in the remaining half usually within one or two years

RELATION OF FOLLOW UP BLOOD PRESSURE OBSERVATIONS TO SUBSEQUENT ANGINA PECTORIS, HEART FAILURE CORONARY OCCLUSION AND DEATH

	No	Angina Pectoris	Heart Failure	Coronary Occlusion	Death
Hypertensive	140	102 (73%)	37 (26%)	33 (24%)	23 (16%)
Normal					
Previously hypertensive	25	18 (72%)	5 (20%)	9 (36%)	6 (24%)
Never hypertensive	56	37 (66%)	11 (20%)	9 (16%)	7 (13%)

Follow up observations disclosed that the height of the blood pressure after the attack did not materially influence the incidence or severity of angina pectoris or the frequency of subsequent attacks of coronary occlusion or of heart failure However with regard to each *of these factors the patients who never had had hypertension* fared somewhat better than those who were hypertensive before or after the attack Thus it seems that when a patient has hypertension prior to the attack the height of the blood pressure after recovery has no prognostic significance However the degree of recovery was generally more complete and the frequency and severity *of heart failure less among patients* who had never had hypertension This is probably attributable to the lower incidence of cardiac enlargement

Atypical Cardiac Infarction G F Strong[1] (Vancouver) states that the possibility of *atypical cardiac*

(1) Can M A J 47 460 463 November

existing heart condition or causes sudden death According to all interpretations of justice such an assumption would necessitate the irrevocable proof that the person in question had not engaged in comparable activities within a reasonable period antedating the coronary occlusion The authors also stated From a compensation standpoint the previous existence of symptomless lesions predisposing to the development of heart strain is immaterial As an accidental development the liability for the sudden disability falls upon the acute stress or the immediately exciting cause This provision existent in many decisions merits little consideration except to emphasize again their inadequacies and injustices A complete reversal of philosophy in this problem is imperative whereby the burden of proof is placed on the plaintiff rather than on the defendant It must be recognized that pursuance of a person s usual occupation even though it is fraught with physical stresses and strains certainly does not involve an undesigned sudden and unexpected event Occurrence of coronary thrombosis is usually unexpected but as already emphasized it is the climax of a pathologic process which has been present for a considerable period

[Until the facts stressed in this article are recognized by compensation boards referees and lawyers the placement of persons with cardiac conditions in industry is going to be a difficult problem —Ed]

Coronary Occlusion Carter Smith II Cliff Sauls and James Ballew[3] (Emory Univ) studied 100 patients (85 men and 15 women) Analysis of the subsequent clinical course showed 54 well 12 ill and 34 dead The clinical course on the basis of age groups in decades is shown in Table 1 There was an immediate (within 21 days) mortality of 12 per cent and a total (immediate and subsequent) mortality of 34 per cent in the series Sixteen patients died in subsequent attacks of coronary occlusion four died of subsequent congestive heart failure and two died of unrelated causes Twenty five patients had recurrent attacks and in all but three these

(3) A I t M d 17 681 69 O t be 194

in the aging process Its progressive tendency is admitted, and countless instances of its premature occurrence are common knowledge Therefore, precipitation or sudden closure of a coronary artery, already conditioned by a gradually progressive and definitely preexisting pathologic process cannot justly be related to certain acts which may occasion temporary increased work for the heart Identical strains in the past did not eventuate in this tragedy This contention is further supported by the fact that coronary thrombosis occurs with greater frequency among persons engaged in sedentary occupations than among those performing manual tasks In fact many instances of coronary thrombosis occur during rest and sleep

Frequently advanced is the argument that strenuous exercise conceivably evaluated as designating an injury is capable of damaging the normal heart This contention lacks pathologic confirmation There remains little doubt that many prevailing court decisions governing so called injuries in the occurrence of coronary thrombosis are based on political prejudice rather than on scientific facts M H Kahn and S Kahn have implied this fact in stating *In harmony with the liberal interpretation of the compensation laws we must assume for practical purposes that strain of the healthy heart is possible There is no reason why the medical profession should abet an erroneous concept in order to harmonize with legal interpretations Lawmakers should be properly advised as to the true issues involved There is little doubt that certain medical testimony already recorded has been erroneous yet has been accepted as the basis for legal precedent Such testimony should be reviewed and corrected*

Kahn and Kahn further stated *In relation to heart strain 'accident in the meaning of the compensation law is held to include some unexpected or unforeseen occurrence of physical or physiologic nature arising out of and in the course of a workman's employment which produces a disabling heart condition*

cent following cardiac infarction In this series the relation of hypertrophy and hypertension was not clear but there was definite correlation between cardiac hypertrophy and mortality rate Both immediate and subsequent mortality was increased among those with cardiac hypertrophy

Some degree of arteriosclerosis could be demonstrated in 79 per cent of patients In most (76 per cent) it was not marked in the large palpable vessels There was little demonstrable relation hip between the degree of peripheral arteriosclerosis and the mortality of coronary occlusion This indicates that the degree of arteriosclerosis or atherosclerosis in the coronary arteries could not be determined from that manifest in peripheral vessels

Early diagnoses and proper treatment of the immediate attack should materially reduce morbidity and mortality In a patient with suspected coronary occlusion absolute bed rest should be maintained until true diagnosis is established Two or more electrocardiograms should be made during this observation period Often an interval of five to seven days is necessary before the electrocardiogram will confirm or disprove the suspected diagnosis Occasionally longer periods are necessary In this series one patient did not show positive electrocardiographic changes until 15 days had elapsed and in another characteristic changes were not found until the fifth week The finding of a leukocytosis and an increased sedimentation rate often help in establishing correct diagnosis

came within two years after the initial attack Fifteen of the 25 patients died in the subsequent attacks This mortality rate of 60 per cent is almost double that of the initial attacks (34 per cent)

Among these patients occupations involving executive capacities or considerable individual initiative were the most frequent Overworry overwork and overeating were the commonest habit excesses obesity, chronic cholecystitis and diabetes mellitus the most commonly associated diseases physical exertion bed rest large meals and emotional upsets the most frequent events associated with the immediate attack and circulatory collapse and embolic phenomena the commonest complications of the immediate attack.

TABLE 1 —CLINICAL COURSE OF DIFFERENT AGE GROUPS IN DECADES

	20 30	30-40	40 50	50-60	60 70	70 80	TOTAL
Living	0	3	17	30	10	6	66
Dead	1	1	7	10	13	2	4

Youngest patient 8 oldest, 78

Abdominal fulness and epigastric distress occurred in more than half of the patients (Table 2) and was in some the most difficult of all symptoms to control Analysis of referred pain in 46 patients of the group showed it in practically all points that have previously been described

TABLE 2 —REFERRED PAIN AND ABDOMINAL DISTRESS IN 100 PATIENTS WITH CORONARY OCCLUSION

Epigastrium	14
Elbows or arms	[illegible]
Shoulders	4
Cervical vertebrae	2
Lumbar vertebrae	1
None (all pain substernal or precordial	3
Data insufficient	54
Abdominal distress	50

Hypertension before the attack was found in 41 per cent of patients it persisted after the attack in 20 per cent Cardiac enlargement was found in 59 per cent Progressive cardiac hypertrophy was [illegible] 10 per

tory tract may result from *mediastinal lymphadenitis* *Penetrating diseases of the aorta* such as dissecting aneurysms rupture of the aorta due to necrosis of the medial coat saccular aneurysm of syphilitic origin etc lead to excruciating pain resembling that seen in certain cases of myocardial infarction

Pain of *duodenal ulcer* may in exceptional cases be felt in the chest and confused with that of angina pectoris Tendency to emphasize significance of location and radiation of chest pain rather than the importance of circumstances under which it occurs is a common cause of errors in diagnosis Ordinarily discomfort associated with *pylorospasm secondary to diseases of the gallbladder* tends to be localized on the right side In exceptional instances these disorders may be associated with pain radiating to the left shoulder and arm Such symptoms frequently result in erroneous diagnosis of angina pectoris an unavoidable error if too much stress is laid on the location radiation and character of the pain rather than on the history of its behavior Discomfort of pylorospasm can often be reproduced by artificial distention of the stomach with air or water *Cascade stomach* may be associated with chest pain of a type readily confused with pain of coronary disease Harrison observed three such cases in all of which the pain responded satisfactorily to measures directed at the gastro intestinal rather than the cardiovascular system In one case of *diverticulum of the stomach* Harrison observed chest pain closely resembling that of angina pectoris in location radiation and character but bearing no relation to effort and having a definite relation to meals In cases of diabetes and coronary arteriosclerosis administration of insulin may precipitate attacks of angina pectoris However it is not generally recognized that chest pain not anginal in type and not associated with a grave prognosis may also occur as result of *dextrose deficiency*

As a general rule any pain in the upper abdomen chest neck shoulders or arms which has a definite relationship to physical exertion should be considered as

PHYSIOLOGIC DIAGNOSIS

Anginal Syndrome

Some Puzzling Aspects of Pain in the Chest Tinsley R Harrison[4] (Bowman Gray School of Med Wake Forest College) lists some conditions commonly confused with coronary thrombosis and angina pectoris *Myalgia and arthralgia in the region of the left shoulder* seldom cause diagnostic difficulty because the pain is related to movements of local parts rather than to general exertion More confusing is muscular' pain in those regions associated with coronary disease probably due to reflex muscle spasm resulting from heart disease In all middle aged and elderly persons complaining of pain in the left arm careful search for angina pectoris must be made even though the pain presents all characteristics of muscular pain *Spinal arthritis* with coronary disease may cause confusion in interpreting pain in the back and the back of the neck A patient with angina pectoris may have substernal distress associated with pain in the back of the neck but occasionally the pain of angina pectoris may occur only in the latter region Relation of pain to walking its relief by glyceryl trinitrate and associated electrocardiographic changes leave no doubt that angina pectoris is present

One type of *pericarditis* which occurs most frequently during the winter and especially in individuals who have had a recent respiratory infection commonly leads to an erroneous diagnosis of coronary thrombosis Onset is usually sudden but the pain is more likely to be stabbing and to be intensified by breathing and is usually less constrictive than the pain of coronary thrombosis Except for this the two conditions resemble each other closely both being associated with fever leukocytosis and somewhat similar electrocardiographic changes Obscure minor substernal pain with infection of the respira

(4) J A M A 1 0 519 5 4 Oct 17 1942

ance of one organ may reflexly via the vagus nerve bring about a concomitant disorder in the other

Patients with angina pectoris as a rule walk with greater difficulty after eating because anginal pain is more readily induced It is caused by the increased work imposed on the heart by the digestive processes as well as by the reflex coronary constriction resulting from gastric distention and contraction Gilbert Fenn and LeRoy succeeded in abolishing or lessening this greater susceptibility to anginal pain after eating by giving atropine Some patients with the combined syndromes of peptic ulcer and angina pectoris walk more freely and farther after a meal In these patients anginal pain developing on effort is a product of the various forces operative at the moment Whether the patient can walk more freely when the stomach is full or empty will depend on which influence is stronger the vasoconstrictor effect on the coronary arteries conditioned reflexly by the gastric distention induced by the meal or the inhibition of the hunger contractions by introduction of food into the stomach and consequent reduction of afferent impulses or of vagal tone

Patients with the combined syndromes of peptic ulcer and angina pectoris when treated for symptoms of peptic ulcer often report relief from the anginal seizures Such patients should receive a modified Sippy diet or some other suitable diet with frequent feedings In addition they should receive full doses of atropine enough to induce dryness of the mouth this necessitates giving 1/150 1/75 gr three or four times a day From ⅓ to ½ gr phenobarbital given thrice daily lessens reflex excitability In some cases alkalis or colloidal aluminum hydroxide may be useful in others these drugs seem to be of less value

Glyceryl trinitrate should be used freely for postprandial pain regardless of location At times erythrol tetranitrate ½ 1 gr four times a day is helpful Theophylline with ethylene diamine gives no relief and may aggravate symptoms by irritating the stomach

angina pectoris until proved otherwise This rule is subject to certain rare exceptions but these are not likely to lead to confusion

Cardiac Pain G F Strong[5] (Vancouver) describes conditions which may cause chest pain and thereby simulate angina pectoris The pain may be caused by disease of the chest wall or of the thoracic or abdominal viscera Thus pain arising in the chest wall as such may be due to such diverse conditions as intercostal neuralgia myalgia, herpes zoster and rarely neurofibromatosis, mastitis or mastodynia as well as inflammation or disease of the ribs, cartilage or fibrous tissue A common source of confusion with real heart disease is the radiculitis resulting from irritation of the dorsal nerve roots caused by arthritis or periarthritis of the vertebral articulations themselves or of the costovertebral joints This may closely simulate angina even to the point of being elicited by exertion and relieved by rest

Visceral diseases other than heart conditions causing chest pain include pleural lesions especially diaphragmatic pleurisy in which no rub is heard, and pulmonary disease such as pneumonia bronchiogenic carcinoma and embolism Large pulmonary infarcts often resemble cardiac infarction closely Inflammation stricture spasm or neoplasm of the esophagus may cause chest pain and closely associated therewith are mediastinitis and mediastinal tumor Lesions of the stomach and gallbladder and diaphragmatic hernia may also cause confusion

Angina Pectoris and Syndrome of Peptic Ulcer Hyman Levy and Ernst P Boas[6] (Mount Sinai Hosp New York City) interpret experimental and clinical evidence as suggesting that the common denominator of the syndromes of angina pectoris and peptic ulcer is heightened excitability of the vagus nerve Symptoms of peptic ulcer may arise from vagal activity in the stomach and those of angina pectoris may result from vagal coronary vasoconstriction A functional disturb

(5) Canad M A J 48 318 322 April 1943
(6) Arch Int Med. 71 301 314 M 1943

could be discontinued These considerations emphasize the importance of individualizing each case and of giving an adequately long course of treatment

Four patients were studied by means of exercise tolerance tests before and during treatment to obtain quantitative measurements of their improvement In each the amount of exercise before development of an anginal attack was markedly increased under testosterone therapy, and the severity of the attacks as measured by duration of pain was correspondingly diminished In each case subjective improvement was reported before quantitative changes could be demonstrated

Section of the Posterior Roots for Relief of Pain in Angina Pectoris Observations on five cases lead Hall Haven and Robert L King[8] (Seattle) to conclude that

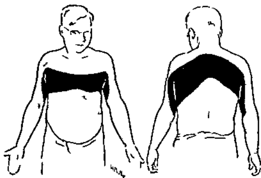


Fig 6 —P t t 14 m th ft p at n D tt d ry l b th t h nd p n ld p n s ly b t

intradural section of the first five thoracic posterior roots effectually severs all cardiac afferent fibers concerned in production of anginal pain The operation can be performed largely with local anesthesia and seems less shocking than an equivalent paravertebral rami section The only fatality in this series occurred in a patient with consistently low blood pressure and extreme arterio

(8) S g Gyn & Obst 75 08 19 A gu t 1942

The rigidity and duration of this regimen vary in each case In the presence of peptic ulcer or of symptoms suggesting advanced coronary narrowing and imminent coronary occlusion treatment must be prolonged If it is suspected that coronary closure is occurring the patient should be put to bed and treated as for coronary thrombosis Sudden change in the provoking causes of anginal pain with change from angina pectoris after effort to anginal attacks at rest, indicates a progressive lesion in the coronary arteries and heralds development of cardiac infarction Rest and use of vasodilators and an ulcer regimen may relieve the coronary insufficiency in these cases and allow establishment of sufficient collateral circulation to enable the patient to survive closure of the particular coronary artery whose progressive closure is at the root of exacerbation of symptoms

Patients who have had peptic ulcer and who subsequently have disease of the coronary arteries may experience anginal pain on effort or the pain of coronary thrombosis only in the abdomen In some cases the pain may start in the abdomen and radiate to the chest or the arms in others it may commence in the chest and radiate to the abdomen This distribution of pain may be due to reflexes initiated by the disturbance in the heart, or the pain may simply travel along nerve pathways previously sensitized by the ulcer

Treatment of Angina Pectoris with Testosterone Propionate Results in 22 patients are reported by Maurice A Lesser[7] (Boston Univ) This agent not only reduces the frequency of attacks but decreases their severity It does not however give immediate relief from an anginal attack as does nitroglycerin Furthermore improvement after use of this drug varies with the patient both in time of onset and in degree Whereas some patients showed improvement after 2 or 3 injections of testosterone propionate others showed no improvement until 10 injections had been given Some required 15 25 injections over months before therapy

(7) N w Engl nd J Med 8 185 189 Feb 11 1

ELECTROCARDIOGRAPHY

Criteria for Differentiating Deep Q_3 Electrocardio grams from Normal and Cardiac Subjects Milton Mazer and John A Reisinger[9] (Washington D C) analyzed 102 electrocardiograms with significantly deep Q_3 waves Of the group of patients represented 44 had myocardial infarction 15 arteriosclerotic heart disease 14 hypertensive heart disease 2 rheumatic heart disease 1 unclassified heart disease 7 hypertension and 19 no evidence of heart disease In 19 records of the organic heart disease group the deep Q_3 was the only abnor mality These records were compared with 19 of the normal group

When the Q_3 electrocardiogram contains abnormal T waves it may be concluded that the deep Q_3 is due to organic heart disease This seems reasonable as the inci dence of fortuitously occurring deep Q_3 waves is only 0 47 per cent in normal individuals When the Q_3 is the only abnormality a decision as to its significance is often impossible though the position of the heart may be of presumptive assistance It is known that factors causing the heart to assume a more transverse position will pro duce a deep Q_3

Analysis of the electrocardiograms reveals that deep Q_3 deep Q_2 high T_1 or high T_4 waves are more likely to occur in Q_3 tracings of patients with organic heart disease However none of these factors alone can dif ferentiate the abnormal from the normal cases in a sufficient number of instances It was therefore decided to set up criteria involving all four factors and to apply them to those records in which the deep Q_3 was the only abnormality The criteria selected were (1) Q_3 of 75 per cent or more of the highest P wave (2) Q_2 of 1 mm or more (3) T_1 of 3 mm or more and (4) T_4 of 4 mm or more

The 38 records with no abnormality other than the

(9) Am J M S 206 48 53 July 1943

sclerosis This combination may be considered a contraindication to use of this procedure, as may marked congestive heart disease Patients who can be satisfactorily controlled by medical means should not be subjected to the operation Alcohol injection is safer and preferable in most instances However, for patients with intractable angina pectoris in whom alcohol injection is unsuccessful and for that small group of exceptionally favorable risks in whom it is desired to avoid the 25 per cent chance of a poor result following alcohol injection this procedure is the method of choice

Of four patients followed for one to five years none has had any semblance of painful anginal attacks since operation Each experiences some definite subjective manifestation that warns him when he reaches his tolerance of exertion This seems in general to be a vague sense of fulness in the neck and chest, with an accompanying feeling of apprehension In all cases there was definite and marked improvement in the tolerance for exercise Each can now do more before noting the 'warning signal' than he could previous to operation before experiencing pain This may constitute evidence of improved coronary circulation Figure 62 illustrates the area of sensory loss occurring in one case after operation

nary and may be treated as an accidental injury even though the exertion was intentionally made (3) War risk insurance The veteran must prove that he suffered a service connected total and permanent disability before his policy lapsed for nonpayment of premiums (4) Life health and accident insurance If the assured before applying for his policy had heart disease and concealed this fact the insurer may cancel the policy on the ground of breach of warranty or fraud If the heart disease develops after the policy is taken out the assured is entitled to payment of benefits The doctor must decide whether the assured actually has heart disease and whether it prevents his earning a living

The alleged injurious stimuli relied on in legal claims for cardiac disability are (1) direct trauma to the heart (2) indirect trauma due to excessive demands on an impaired heart (3) exposure of the heart to noxious agents and (4) injuries due to psychosomatic stimuli If after collapse at work weeks or months elapse before appearance of the final injury imputed to the stimulus serious problems of proof arise Here the electrocardiogram may be of great benefit by providing completion evidence It may produce objective evidence immediately after collapse and at intervals thereafter which will be of value in helping to prove or disprove the fact and continuity of causation It would seem wise that all workmen who collapse at work be hospitalized and initial and interval electrocardiograms made

In the usual medicolegal case the physician will be asked whether the described stimulus in light of all available facts was a probable cause of cardiac disability He may be asked to give a diagnosis and prognosis He must refrain from testifying if he feels the subject beyond his professional attainments As an expert witness he may be called on to testify in two possible ways His opinions may be based on personal knowledge of the case or on hypothetical questions

A physician who proposes to give an electrocardiographic interpretation must have his expert qualifica

deep Q_3 were restudied to determine how many of these criteria were satisfied by each Each record was given a value equal to the number of criteria satisfied No record satisfied more than three, many satisfied none Tracings for the abnormal group tended to satisfy more of the criteria than the others Only two for the normal group satisfied more than one criterion while 10 of the 19 tracings for the organic heart disease group did. It appears that if an otherwise normal Q_3 electrocardiogram satisfies two or more of the criteria proposed it is more likely to represent a patient with heart disease If it satisfies fewer than two criteria no conclusion can be drawn Since the number of cases in this study is not large, the findings recorded are not meant to be more than suggestive

[Entirely too many diagnoses of coronary artery disease are based on a deep Q wave alone These additional criteria should help in making such diagnoses more justifiable —Ed]

Some Legal Aspects of Heart Disease and the Electrocardiogram are discussed by J E F Riseman and Hubert Winston Smith[1] (Harvard Univ)

The following legal categories are the ones most apt to give rise to cardiac litigation (1) *Tort law If A intentionally or negligently exposes B to an injurious stimulus causing cardiac injury or disability this will afford grounds for liability in damages* (2) Workmen's compensation claims If employe A suffers injury from an accident arising out of and in the course of employment and his employer carries workmen's compensation insurance A is entitled to receive benefits without proving any negligence or fault An 'accident' must have occurred and must appear to be the probable cause of disability The physician has to determine whether the employe has a cardiac disability whether the stimulus described was adequate to cause cardiac injury and whether it probably did cause the disability The courts hold that if the heart disability is due to some unusual exertion strain or lifting foreign to the normal work done in that type of employment the effort is extraordi

(1) Ann Int Med 19 81 106 July 1943

nary and may be treated as an accidental injury even though the exertion was intentionally made (3) War risk insurance The veteran must prove that he suffered a service connected total and permanent disability before his policy lapsed for nonpayment of premiums (4) Life health and accident insurance If the assured before applying for his policy had heart disease and concealed this fact the insurer may cancel the policy on the ground of breach of warranty or fraud If the heart disease develops after the policy is taken out the assured is entitled to payment of benefits The doctor must decide whether the assured actually has heart disease and whether it prevents his earning a living

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tions established to satisfaction of the court on preliminary examination The attorney will interrogate him concerning his education specialized training experience and current practice The lawyer for the opposing party has a right to cross examine the witness In order that electrocardiograms may be received in evidence certain preliminary steps must be taken to show that the apparatus and technic were adequate and trustworthy and that the results tendered truly state the facts The electrocardiograms so vouched for should be offered in evidence before any opinion is expressed on them

From the standpoint of probative value, electrocardiograms in their proper sphere are of great value because they *substitute objective demonstration* of a uniform character for variable subjective impressions Whenever a physician is to testify regarding electrocardiograms he must acquaint himself and his lawyer with the diverse *conditions which might produce the same or a substantially similar tracing* The electrocardiogram may yield information not obtainable by any other means during life on three aspects of heart disease (1) It may give direct proof of the presence location and type of an abnormal rhythm even if no demonstrable changes are evident post mortem (2) It may give direct evidence of the presence of damage to the heart muscle (3) It may yield indirect confirmatory or illustrative evidence of the presence of certain types of pathologic lesions or the action of certain etiologic agents On the other hand it is *important* to realize that it is impossible to state from the tracing alone that the alleged injury and nothing else resulted in the cardiac damage or that the damage evidenced *in the tracing necessarily* resulted in cardiac symptoms or incapacity or where the electrocardiogram is normal that cardiac damage or symptoms do not exist An abnormal electrocardiogram does not necessarily mean poor cardiac function and cardiac damage does not necessarily show itself in the electrocardiogram

It is unwise to rest the diagnosis of a *heart condition* on the electrocardiogram alone but rather the tracing

should be utilized as part of the total available clinical evidence Its main use is to present objective confirmation of the presence of heart damage and the time relationship between the alleged injury and the development of the cardiac damage It is evident that the elec-

RELATIVE IMPORTANCE OF ELECTROCARDIOGRAM IN DIAGNOSIS OF HEART DISEASE

ETIOLOGY	PATHOLOGY	FUNCTION
Congenital III	Developmental defects III	Congestive failure IV
Rheumatic III		Cardiac asthma IV
Syphilitic III	Valvular damage III	Angina pectoris IV
Arteriosclerotic II	Arterial damage III	Limitation of activity IV
Hypertensive II	Muscular damage	
Asthmatic II	Degeneration or destruction of the	Causes of increase of cardiac symptoms
Thyrotoxic III	myocardium II	Increase in pathologic lesions IV
Pneumonic III	Relative myocardial	
Diphtheric III	weakness (especially in a heart already damaged) IV	Increase in work IV
		Abnormal rhythm I
Toxic II	Pericardial damage II	Bacterial endocarditis
Traumatic II	Abnormal rhythm I	IV

I d gn sis m y be mad by th l t d gram lo e II d gn sis us lly o f equ ntly is confirmed o orroborated by lect d gr phi id ce III d ag m y be ld d by th el ct oc d gr m und m cumst nces d IV d gn is is n t h lp d by th l t d gr m

trocardiogram does not have the same probative value in all instances The several classes of heart conditions which conceivably may confront the examiner are presented in the table

In cases of direct trauma to the heart electrocardiograms may yield objective proof of the existence or development of cardiac damage following injury In cases of alleged indirect trauma initial and interval electrocardiograms are of value In some instances of injuries ascribed to psychosomatic stimuli consisting of nervous shock without substantial impact or other psychic factors electrocardiograms may show definite progression of disease or new pathologic lesions following the emotional strain

Electrocardiogram in Pulmonary Embolism To study the cause of electrocardiographic changes in pulmonary

embolism James Currens correlated electrocardiographic alterations with anatomic abnormalities found in the hearts of 30 patients with pulmonary embolism In selecting subjects preference was given to those who had survived the pulmonary embolism several hours who presented clinical evidence of shock and whose hearts were large and showed coronary sclerosis at autopsy In five recent infarction of the right or left ventricle was found One of these showed recent thrombosis of the right coronary artery with regions of infarction of the posterior portion of the right and left ventricles and interventricular septum In the remaining four recent infarction was noted without demonstrable occlusion of coronary arteries Each patient had shown clinical evidence of shock for 4 to 24 hours following pulmonary embolism In three of the four hearts, regions of recent infarction were found in the right ventricle *The most frequent site of infarction in the left ventricle* in the four cases was the posterior portion supplied by the right coronary artery Infarction of the heart can result from severe prolonged shock without pulmonary *embolism as illustrated by one case in which the patient* was in profound shock for 54 hours following hemorrhage from a syphilitic aneurysm the infarct was in the posterior basal portion of the left ventricle In several cases likewise in which no structural changes in the heart muscle could be demonstrated electrocardiographic changes typical of pulmonary embolism were found

Asphyxia has been *considered a factor affecting* the electrocardiogram in pulmonary embolism Two electrocardiographic tracings of a patient who had had pulmonary embolism 20 hours before are shown in *Figure 63a* and *b* The first tracing was made when oxygen saturation of arterial blood was 74 9 per cent The B L I mask was then attached and the patient was allowed to breathe 100 per cent oxygen 12 minutes later the second electrocardiogram was made at which time oxygen saturation of arterial blood was 89 2 per cent The

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only demonstrable difference in the two tracings was a decrease in pulse rate from 107 to 100 The observation suggests that a decrease in oxygen saturation of arterial

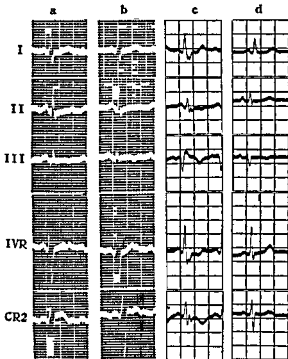


Fig 63 —El t c d rr m d b 4 h aft pulm ry mbol m pp bl h g t gs fter ter l yg n t t w i d f om 74 9 (a) t 89 2 (b) p t h t t d d f m 107 t 100 T g h ft p lm y mb l m w d S p tt w th QRS mpl m u g 0 1 d du t n f QRS mpl d d t turn t 0 10 d f th d j d S m th m th l t T w n l d CR w s l t t t n t n rm l

blood alone does not affect the electrocardiogram in cases of pulmonary embolism

In appraising the electrocardiographic changes during suspected pulmonary embolism it should be remembered that no one electrocardiographic abnormality is con

sistently present in pulmonary embolism From a study of 25 cases in which the electrocardiograms were altered definitely it was evident that the precordial leads (IV R CR_2 and Wolferth) are of definite diagnostic aid in certain cases since in 28 per cent the only abnormality was in these leads Of particular value are the CR_2 and Wolferth leads Pulmonary embolism tends to increase duration of QRS complex if the tracing is made 1 24 hours after onset In several electrocardiograms studied duration of the QRS complex was increased but in only one was it abnormal (*Fig 63c and d*) the electrocardiogram demonstrated a transient impairment of intraventricular conduction measuring 0 12 sec which returned to normal after three days

Strain on the right ventricle seems to be the dominant factor in electrocardiographic changes in pulmonary embolism Presence of a pulmonocoronary reflex following pulmonary embolism is difficult to prove and it seems likely that any compromise in the coronary circulation is best explained by shock and increase in pressure in the right side of the heart The decrease in blood flow to the right ventricle from decrease of arterial pressure gradient plus an increase in work of the right ventricle may account for the occasional association of angina pectoris with pulmonary embolism

Significance of Electrocardiographic Changes in Malignant Hypertension was studied by J David Markham and Nathan Bloom[3] (Med College of Virginia) Willius was among the first to indicate that hypertensive heart disease causes a change in the T wave He found that in cases exhibiting T wave negativity in lead I or in leads I and II the predominant disease was hypertension This was not true of other combinations of T wave changes Barnes and Whitten found that where lesions increased the work of the left ventricle inversions of the T wave were often present in lead I, or in leads I and II similarly right ventricular preponderance produced T wave inversion in leads II and III

(3) J Lab & Clin Med 7 1156 116 June.

although correlation was not as close as in left ventricular preponderance In nearly two thirds of their patients with simultaneous inversions of the T wave in all leads there was no evidence of ventricular preponderance and they concluded that the factors producing ventricular preponderance were not the same as those producing T wave inversions They hypothesized further that the changes evidenced ventricular strain and were not dependent on size of the heart

The authors study was divided into several parts (1) Consideration of predominant trends in electrocardio

TABLE 1—RELATIVE INCIDENCE OF PREDOMINANT CHANGES IN THE ELECTROCARDIOGRAMS OF 37 PATIENTS WITH MALIGNANT HYPERTENSION (54 EKG)

Changes (low flat diphasic or negative) in T T or T and T	75 9%
Deep S or S and S	69 3%
Left axis deviation	59 3%
Depressed S T$_1$, S T or S T and S T	50 0%
Deep S	46 3%
Depressed S T S T or S T and S T and negative T T or T and T	33 3%
High voltage R$_1$ R or R and R	24 1%
Elevated S T	16 7%
Depressed S T S T or S T and S T with upright T complexes in those leads	14 8%
Q wave lead I	14 8%

grams of 37 patients who died of malignant hypertension (Table 1) revealed that 75 9 per cent of electrocardiograms showed abnormalities of the T wave in lead I and/or lead II Left axis deviation was present in 59 3 per cent and depression of S–T segment in lead I and/or lead II in 50 per cent These results show that in malignant hypertension variations in T waves and S–T segments must be considered concomitants of the disease When S–T depression is associated with abnormalities of the T wave there is a more severe effect of the disease on the heart than T wave changes alone would indicate (2) Study of the correlation of T wave changes to myocardial damage as proved at autopsy (Table 2) showed positive correlation in 68 75 per cent of cases (3) Four

teen patients were available for analysis of cardiac weight Cardiothoracic ratio was determined in nine of them before death Mean cardiac weight was 586 Gm. and mean cardiothoracic ratio 55 per cent Deviations from the mean were considerable the smallest heart weighed 400 Gm and the largest 820 Gm, and cardiothoracic ratio ranged *from 45 to 66 per cent* Data in 20 cases in which cardiothoracic ratio was known revealed

TABLE 2.—CORRELATION OF T WAVE CHANGES IN LEADS I AND/OR II WITH PRESENCE OR ABSENCE OF MYOCARDIAL DAMAGE AT AUTOPSY (16 CASES)

	Cases	Per Cent
Damage with EKG changes	7	43.75
Damage without EKG changes	[illegible]	12.50
EKG changes without damage	3	18.75
No damage and no EKG changes	4	5.00

Positive correlation is present in 68.75 per cent of cases and negative correlation in 31.25 per cent While these figures are derived from too small a series to prove the point beyond question they confirm the impression that T wave changes in malignant hypertension are due to myocardial damage and not to enlargement of the heart

a similar range 15 of these showed T wave changes indicative of myocardial damage Electrocardiograms of five patients covering the entire range of cardiothoracic ratios showed no T wave changes These findings suggest there is no definite correlation of cardiac size and cardiothoracic ratio or of electrocardiographic changes and cardiothoracic ratio The cardiothoracic ratio is therefore a totally unreliable guide in interpreting changes in electrocardiograms

To study prognostic significance of the changes observed the authors analyzed *27 electrocardiograms of 11 patients who had more than one taken before death* with special reference to changes in S-T segments and T waves Eighty one per cent showed characteristic S-T or T wave changes in at least one electrocardiogram There was no uniformity in the interval between appearance of the characteristic electrocardiogram and death However *appearance of these changes meant* that the kidneys were *on the verge of complete failure and death* was near A tabulation of the age at which each patient died showed that the greatest mortality the 37

patients was in the 35 39 year group Most deaths oc curred after 20 while none occurred after 50 This indi cates that the electrocardiogram is a reliable guide in following the progress of malignant hypertension and has some prognostic value

This study suggests that low flat diphasic or negative T waves and depressed S–T segments are characteristic in lead I lead II or leads I and II of the electrocardiogram in malignant hypertension

Wolff Parkinson White Syndrome This syndrome affects individuals of any age but is generally found in the young accompanied by paroxysmal tachycardia It may appear or disappear spontaneously Physical ex amination and radiography may reveal a normal heart or one with various cardiopathies

Rodolfo Dassen[4] presents a case

Man 21 without familial cardiac history had attacks of palpitation for the past 10 years whenever he played foot ball During these attacks he felt nauseated and faint and his vision was clouded for two or three minutes He felt no pain but there was throbbing in the precordial region and throat After violent exercise he had five or six attacks in a half hour Physical examination revealed cold and cyanotic hands the heart was not enlarged but there were tachycardia and cardiac frequency of 180 Arterial and venous throbbing in the neck was clearly visible A teleroentgenogram showed a heart of normal configuration and size Basal metabolic rate was +4

Quinidine sulfate was given four times daily over a period of months daily dosage varying from 0 50 to 01 20 gr Despite the large doses of quinidine the extrasystoles could not be pre vented Bundle branch blo k was diminished and there was less depression of S–T segment No conclusion was reached as to whether this was due to the drug or to a myocardial rest

In case of reaction quinidine therapy should be stopped In case of block digitalis is usually contrain dicated

The Wolff Parkinson White syndrome should be con sidered a benign condition unless accompanied by car diopathy In general prognosis is good The factor of greatest importance is the state of the heart This is a

(4) M d B Aires 19 04 J u y 194

functional rather than an organic disorder, there is a constitutional disturbance with or without anatomic bases in the normal mechanism of inception of motion and conduction of the cardiac cycle Cases without curves of the block type and without tachycardia should not be considered cases of the Wolff Parkinson White syndrome Dassen states that *no satisfactory explanation* of the syndrome has as yet been offered He credits the *short P–R of the electrocardiogram* to an auricular *focus near the nodule (Pezzi)* or node (Katz)

TREATMENT

Cardiac Resuscitation Samuel A Thompson, George L Birnbaum and Irving Shiner[5] (New York City) believe that any attempt at cardiac resuscitation is *always* justified Many such attempts have been successful even after considerable periods of inactivity have elapsed, Adams recently reported a 20 minute cardiac arrest with complete recovery The authors report a case of successful resuscitation with operative recovery of the patient following cardiac cessation due to auricular and ventricular fibrillation In this instance massage plus the possible benefit of neosynephrin and pulmonary ventilation were successful

Cardiac resuscitation must be done quickly and with a definite plan in mind First and most important is the establishment and maintenance of proper pulmonary ventilation When cardiac arrest follows civilian injuries repeated sharp blows with the fist over the precordium will sometimes induce cardiac contractions During abdominal or thoracic operations, massage of the ventricle should be instituted Intracardiac injection may be of value The site of injection is important and should be in the right auricle Approach to the right auricle is through the third or fourth intercostal space on the right side, close to the sternum and the needle is inserted in a downward and inward direction The

(5) J A M A 119 1479 1485 A r 29 1942

needle should be about 4½ in long Epinephrine is probably the most efficacious of the drugs used with this procedure but if no drug is available the needle alone should be used for the action current of injury thereby produced may be sufficient to produce cardiac contraction If an electrical apparatus of the pacemaker type is available it should be used as soon as possible This is also applied to the right auricle for best results

New Adrenalin Like Compounds Their Action and Therapeutic Application M H Nathanson[6] (Univ of Southern California) discusses the therapeutic uses of paredrine and benzedrine Both are stable compounds having a prolonged action and are effective on oral administration

Paredrine has an active cardiovascular effect and is useful in prevention of cardiac or ventricular standstill The two most common conditions in which syncope due to cardiac standstill occur are (1) the ventricular standstill associated with heart block and (2) the cardiac arrest associated with a hypersensitive carotid sinus In cases of heart block in which attacks of syncope are frequent adrenalin is still the drug of choice and a subcutaneous injection every three to four hours should increase ventricular irritability sufficiently to prevent ventricular standstill In cases of chronic heart block with infrequent syncopal attacks a drug effective on oral administration is desirable A dose of 40 to 60 mg paredrine three to four times daily usually lessens the tendency to cardiac standstill This applies also to the syncope associated with a hyperactive carotid sinus In some instances this dosage must be increased

Benzedrine is the most powerful central nervous system stimulant of the adrenalin like compounds It is of value in a variety of clinical conditions including narcolepsy mental depression chronic exhaustion and obesity Benzedrine is of definite value in orthostatic or postural hypotension. It may however produce symptomatic relief without influencing the postural effect on

(6) C lifornì & W t M d 57 301 307 N ember 194

the blood pressure It is probable, therefore, that the drug exerts its effect in this condition through its central action

Magnesium Sulfate in Paroxysmal Tachycardia Linn J Boyd and David Scherf[7] (New York Med College) studied the effect of intravenous injections of magnesium sulfate in 10 cases of paroxysmal tachycardia and 1 case of flutter A 10 per cent solution was beneficial in three of eight attacks No failures occurred when a 20 per cent solution was used in eight attacks so this concentration in doses of 15 to 20 cc is recommended About 30 seconds should be taken for the injection If the drug is injected too slowly it may not reach the heart in sufficient concentration to be effective

No untoward effects were observed Disturbances of conduction and ventricular extrasystoles appear for a short time after injection The rate of paroxysmal tachycardia frequently diminishes before tachycardia disappears The authors advise against the use of magnesium sulfate intravenously when marked myocardial damage is obvious or marked intraventricular conduction disturbances or gallop rhythm are present

Some Clinical Uses of Papaverine in Heart Disease Stephen R Elek and L N Katz[8] (Michael Reese Hosp Chicago) state that oral administration of papaverine in heart disease is indicated (1) in patients with the anginal syndrome and (2) for eradication of premature beats Its use intravenously is indicated for temporary abrogation or diminution of frequency of premature systoles when these constitute a hazard e g following a myocardial infarct and to alleviate a severe paroxysm of anginal pain There is no contraindication to its use except possibly intravenously in complete auriculoventricular block

Papaverine should be used in doses larger than those conventionally recommended Orally 1½ gr doses three or four times daily proved highly successful in

(7) Am J M Sc 206 43-48 July 1943
(8) J A M A 120 434-441 Oct 10 194

about 75 per cent of 17 intensively studied patients with the anginal syndrome Intravenously 1 1½ gr doses cause temporary abolition or reduction in number of premature systoles the effect lasting 2 10 minutes It appears to be more successful in suppressing ventricular premature beats than auricular ones For this purpose it may be given in divided doses or in continuous intravenous drip diluted in saline or saline dextrose solution Orally doses up to 3 gr four or five times a day had a decided effect in eradicating or reducing frequency of premature auricular nodal or ventricular systoles in five patients In this respect its favorable action is comparable to that of quinidine

Papaverine is superior to quinidine because it is a potent and lasting coronary vasodilator may be given intravenously in large doses with a wide margin of safety has a mild sedative action is not a myocardial depressant and does not cause the toxic signs sometimes resulting from quinidine Its only toxic effects are the occurrence of sleepiness when given orally in large amounts and of transient intraventricular and auriculoventricular block and occasionally transient ectopic rhythms previously absent both lasting less than one minute when given intravenously It does not seem to produce narcotic addiction

Routine Use of Cedilanid in Clinical Practice is discussed by Aaron E Parsonnet and Arthur Bernstein[9] (Newark Beth Israel Hosp) Experimentally it has been shown that cedilanid has a greater margin of safety than other Digitalis lanata glycosides and also brings about greater cardiac efficiency It has also been shown that it will not produce a significant reduction in coronary blood flow Fahr and LaDue used the drug on a large group of patients When auricular fibrillation was present its action was rapid and effective They observed that in congestive heart failure its action was excellent even in the presence of normal sinus rhythm They also obtained good results in auric

(9) Am H rt J 6 39 41 J ly 1943

ular paroxysmal tachycardia and auricular flutter and concluded that cedilanid is less toxic in many instances than Digitalis purpurea Sokolow and Chamberlain concluded that the rapid absorption constant potency and rapid action of cedilanid gave it definite advantages over Digitalis purpurea

The authors studied the action of cedilanid in 100 patients The average total oral dose for digitalization was 15 20 tablets (7 5 10 mg) When the rapid and massive method of digitalization was used the total dose was 10 15 tablets (5 to 7 5 mg) The average maintenance dose was 1 3 tablets daily (0 5 1 5 mg) The response of 98 per cent of the group to the oral administration of cedilanid was excellent Only two patients could not be controlled by the oral administration both responded well to whole leaf digitalis

Studies on Purified Digitalis Glycosides Single Dose Method of Digitalization Harry Gold Nathaniel T Kwit McKeen Cattel and Janet Travell[1] (Cornell Univ) studied absorption of digitalis preparations relation between intravenous and oral doses and local emetic action of various digitalis materials Observations were made on over 300 cardiac patients some ambulant and others hospitalized The authors also studied absorption and local irritant action in the cat In 213 patients with varying grades of heart failure who had been without digitalis for at least three weeks and then were given a single dose of 1 26 mg *digitoxin* the only toxic effects were those referable to the gastro intestinal tract (see Table) Of the entire group 2 3 per cent showed nausea (none vomited) in an average of 1 hour 20 minutes in all probability a local action A similar number had gastro intestinal symptoms in an average of 14 hours due obviously to systemic action For comparison 16 specimens of digitalis leaf or tincture were given in a single dose averaging 15 1 cat units, to 161 patients As with digitoxin the only toxic effects were referable to the gastro intestinal

(1) J A M A 119 9 893 Jul 18 '94

tract Incidence of nausea and/or vomiting due to local action in less than 2 hours was high rising from 2 3 per cent with digitoxin to 19 3 per cent with digitalis

COMPARISON OF LOCAL EMETIC ACTIVITY OF DIGITALIS AND DIGITOXIN IN MAN

	DIGITALIS	DIGITOXIN
Patients	161	213
Dose		
Grams	0 89 (0 4 2 4)	1 6 mg
Cat units	15 2 (7 2 30)	3
Nausea and/or vomiting from local action		
Cases	31 (19 3%)	5 (2 3%)
Dose		
Grams	0 80	1 6 mg
Cat units	15 1	3 0
Time to effect	1 7 hr	1 3 hr
Nausea from local action		
Cases	18 (11 %)	5 (2 3%)
Dose		
Grams	0 81 (0 4 1 2)	1 26 mg
Cat units	14 (7 19 8)	3
Time to nausea	1 9 hr (10 min 5 hr)	1 3 hr (0 min. 2 hr)
Vomiting from local action		
Cases	13 (8 1%)	0
Dose		
Grams	1 0 (0 6 1 9)	0
Cat units	16 3 (10 3 6)	0
Time to vomiting	1 5 hr (5 min 3 hr)	0
Nausea and/or vomiting from systemic action		
Cases	8 (5%)	5 (3%)
Dose		
Grams	1 3 (0 73 2 4)	1 6 mg
Cat units	18 9 (13 3 30)	3
Time to effect	14 hr (9 20)	14 hr (8 16)

A ton w s a sum d to b loc l if it curr d n 2 hours nd if l ttl l w g f e t i l t h d t k n pl I th e of d git l tw p tent a e i lud d in whom th i t rv l w th and fi h s respect ly be use gi gibl l wi g h d o urr d t th t m v mting pp ed i d t g l ttl b rpti

Local emetic action was encountered with both tincture and leaf

The authors conclude that the average full oral digitalizing dose of digitoxin is 1 26 mg (3 cat units) as against 15 cat units for digitalis leaf or tincture Absorption of digitoxin from the gastro intestinal tract is

almost complete, oral and intravenous full digitalizing doses are for practical purposes identical Only about one seventh to one third of the potent material in digitalis leaf or tincture is absorbed from the gastrointestinal tract in man The high incidence of gastrointestinal disturbances by local action after administration of digitalis leaf and tincture is probably due to the large amount of cardio active glycosides that must be given when preparations are imperfectly absorbed although some impurity may play a part Local emetic action of large doses of digitalis and of the poorly absorbed purified glycosides precludes their routine use in the single dose method Digitoxin in a single full oral dose digitalizes a patient safely and rapidly in a few hours rather than in the days required by the divided dose method in which digitalis is customarily used

Intravenous Use of Digitalis Glycosides John S La Due (New Orleans) compared the results of oral and intravenous administration of a cardiac glycoside (lanatoside C) to 202 patients with heart disease The drug was given intravenously to 117 patients and orally to 85 In no instance was intravenous use detrimental and in only four cases were nausea and vomiting noted as a transient toxic reaction

The heart rate of patients with auricular fibrillation was controlled much more rapidly by intravenous than by oral administration There was no statistically significant difference in the rapidity of improvement of the other objective signs of heart failure in patients who received the drug intravenously but these patients felt better within two or three hours after injection rested more easily and appeared stronger than did patients who took the drug orally

Measurements of the diastolic heart size and cardiac output by roentgenkymography give strong support for intravenous use of digitalis glycosides These studies showed that intravenous administration of la

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natoside C to patients with heart failure accompanied by normal sinus rhythm usually resulted in a decrease in diastolic heart volume and an increase in stroke output i e an improvement in the mechanical efficiency of the failing heart Moreover this improvement occurred within two hours Hence it seems reasonable to propose that patients with severe congestive heart failure be rapidly digitalized by the intravenous route

Such preparations as strophanthin digitoxin thevetin and scillaren A and B have been adequately standardized and are available In LaDue s opinion lanatoside C may be given intravenously with but slight possibility of untoward results Four patients who alleged that they had never taken digitalis were given 8 cc lanatoside C intravenously The following day it was learned that all had been fully digitalized on entry yet the only sign of toxicity was transient nausea in one patient This suggests that lanatoside C has a wide margin of safety but of course the drug should be cautiously administered to any patient who has been taking digitalis

Physicians planning to give cardiac glycosides intravenously should familiarize themselves with the peculiarities of any chosen preparation since the dosage cat unit potency and toxicity vary widely and are poorly correlated

Combined Use of Strophanthin K and Digitalis in Treatment of Congestive Heart Failure Strophanthin K is a relatively new therapeutic agent and is not to be confused with strophanthin G or ouabain It is an amorphous glycoside derived from Strophanthus kombe while strophanthin G is a crystalline glycoside derived from Strophanthus gratus The crystalline strophanthins have greater toxicity and consequently a smaller therapeutic range than the amorphous strophanthins

When strophanthin K is given intravenously it acts within a few minutes and is almost wholly excreted within 24 hours Digitalis on the other hand is slow in action and its rate of absorption and excretion is pro

longed These properties of the two drugs constitute the rationale of their combined use for as the action of strophanthin begins to wane, the digitalis begins to exert its maximum effect and becomes the cardinal therapeutic agent

John L Garcia and Bernard A Goldman[3] (Louisiana State Univ) studied the combined action of these drugs on 18 patients with congestive heart failure 6 with pure arteriosclerotic heart disease, 3 with hypertensive heart disease 5 with combined hypertensive and arteriosclerotic heart disease 3 with syphilitic heart disease and 1 with thyrotoxic heart disease Ages ranged from 27 to 76 years None had received digitalis for at least 10 days

Each patient was given intravenously, 0 25 mg strophanthin K diluted with 10 cc physiologic saline, over a three minute period Slow administration was used to allow complete fixation of the drug by the myocardium Immediately 6 9 gr digitalis leaf was given orally followed by 3 gr three times daily until the patient was digitalized The usual symptomatic and supportive care was also given

The criteria of recovery from heart failure consisted of disappearance of dyspnea rales cyanosis and edema diminution in the size of the liver and return of the venous pressure and circulation time to normal

Fifteen of the patients were completely relieved of their heart failure Two patients died, one of uremia and the other of embolism but both had recovered from their heart failure before death One patient with an aortic aneurysm compressing the pulmonary artery failed to respond

The average time for the right side of the heart to compensate was 3 1 days and for complete compensation 5 5 days All patients noted subjective improvement within the first two to six hours this was progressive and closely paralleled objective signs or improved cardiac function There were practically no un

(3) Am Heart J 6 20 3 July 1943

toward toxic manifestations aside from the nausea and occasional vomiting associated with full digitalization Electrocardiograms failed to show any detrimental effects on the conduction mechanism or on the state of the myocardium

Maintenance Treatment with Digitalis As a result of Gold s statement that only about 15 per cent of cardiac patients owe to the habitual use of digitalis the fact that they are able to carry on with a reasonable degree of comfort and that the reputation of the drug is not enhanced by its use in the remaining 85 per cent Alfred S Rogen[4] decided to determine whether he had been unduly liberal in dispensing digitalis to patients kept on maintenance doses in some cases for over four years

The first 20 patients who attended the clinic on and after a certain date were chosen The drug was stopped and if objective signs of heart failure appeared it was concluded that lack of digitalis was being felt If without objective evidence the patient complained of not feeling well he was given lactose tablets to make certain that the ill health was not due to psychologic disturbance from want to medicine Only when objective signs of failure appeared was digitalis therapy started again

Ages of the patients varied from 20 to 70 years and duration of digitalis administration from a few weeks to over four years There was a definite history of rheumatic fever in all but three in whom arteriosclerosis with hypertension appeared to be the etiologic factor All had been inpatients with definite signs of cardiac failure Auricular fibrillation was present in all but two The daily maintenance dose varied from ½ to 4 gr of the powdered leaf

Sixteen showed objective evidence of progressive cardiac failure before any complaint was made of ill health or distress in each case compensation had been satisfactory the previous week The time taken for the

(4) [illegible] 694 695 Ju 5 1943

signs to appear after suspension of digitalis varied from 2 to 11 weeks, with an average of just under 5

TIME TAKEN FOR SIGNS TO APPEAR AFTER CESSATION OF DIGITALIS ADMINISTRATION

Age	Maint Dose Gr	Signs	Time After Cessation of Digitalis Wk
45	2	C	5
38	1½	D O	8
41	[illegible]	D O	8
40	2	T	[illegible]
34	4	C T	11
49	[illegible]	D T	6
38	3	D T	2
27	4	O T	6
61	1½	D T	2
54	3	T	4
44	2	T	4
[illegible]	2	O	2
48	3	C D O T	5
47	2	T	4
29	3	T	3
[illegible]	[illegible]	D T	6

C d t cyanosi D v s ble dyspnea O ed ma a d T m k d n ease in heart at

There was no correlation between the size of the maintenance dose age or weight of the patient and length of the sign free period

The remaining four patients made subjective complaints—increased fatigue and a feeling of breathlessness—from two to six weeks after suspension of digitalis but no objective evidence was found to support their complaints Accordingly lactose tablets were given In all four objective signs subsequently appeared from two to six weeks after the first subjective complaint Visible dyspnea was noted in all four increase in heart rate in two and edema cyanosis and liver enlargement in one each These signs appeared in all cases eight weeks after digitalis was stopped Digitalis was restarted as soon as there was any sign of cardiac decompensation with evidence of recovery within a week This fact indicates clearly that digitalis therapy was essential for the comparative well being of these patients

The Effect of the Accumulation of Blood in the Extremities on the Venous Pressure of Normal Subjects was investigated by James V Warren and Eugene A Stead Jr[5] (Harvard Univ) Data are presented in the table The application of venous tourniquets to the upper thigh caused a decrease in venous pressure in

EFFECT OF VENOUS TOURNIQUETS ON THIGHS AT PRESSURE OF 85 MM HG ON THE VENOUS PRESSURE IN EXTERNAL JUGULAR AND ANTECUBITAL VEINS OF NORMAL SUBJECTS

	SUBJ 1		SUBJ 2		SUBJ 3		SUBJ 4		SUBJ 5	SUBJ 6
	Ext Jug	Ant Cub	Ext Jug	Ant Cub	Ext Jug	Ant Cub	Ext Jug	Ant Cub	Ext Jug	Ext Jug
Resting	100	110	100	135	105	110	105	115	80	110
After tourniquets										
1 min.	65	85	80	115	90	100	80	100	70	85
2 min	50	75	60	110	75	100	ι0	100	45	60
3 min.	45	75	45	110	70	105	70	95	46	40
4 min	40	70	40	110	65	105	70	9	5	
5 min	40	70	35	110	65	100	0	100	°5	50
After release										
½ min	95	110		115	100	105	100	115		
1 min.	105	120		125	105		95	110	75	
2 min.	100	1 0		130	105		95		80	110

Values given are venous pressure in millimeters of water

both the external jugular and the antecubital vein The average fall in venous pressure in the external jugular vein was 53 mm water and in the antecubital vein 23 mm water The decrease in venous pressure is greater *in the external jugular than in the antecubital* vein because the arm veins tend to collapse when the venous pressure is lowered After the vein walls are in contact further lowering of venous pressure proximal to the point of collapse produces no further decrease in venous pressure in the distal portion of the vein

Review of Toxic Manifestations of Mercurial Diuretics in Man Arthur C DeGraff and J Ernest Nadler[6] (New York Univ) state that the number of toxic re

(5) Am J M S 05 501 505 Ap il 1943
(6) J A M A 119 1006 1011 J ly 5 194

tion down the arms is that it er ... the diaphragm Also, while anginal pain ... almost anywhere from the jaw to the ... ment it is seldom situated in the ... mary regions i e, between nipple and ...

Duration of pain is also of diagnostic ... Angina lasts roughly 1 30 minutes, ... Pains lasting hours or days are ob... Frequency is also important Thus, ... daily *for months or years* are not due to ... clusion but may be due to spondylitis

Character of the pain may also give ... Variants include tightness fulness ... Angina is a wave of pain, never shooting ... Angina does not change its character ... tient i e, it is never a sharp stab follow ... ache

The most important influencing facto ... exercise or excitement Angina results from ... *anoxia* and comes on during exertion ... *The time factor* is essential in production of ... any muscle Therefore *one must* not be ... *patient* whose pain occurs from walking ... not from walking up two flights of stairs. Other ... which favor production of angina are a full ... cold weather wind anxiety hurry and fatigue ... from these considerations however there is a ... about the degree of exercise which produces ... in the same *patient In* advanced cases the ... come on when the patient is sitting or lying down

Accompanying symptoms in angina are ... salivation urination and occasionally shortness of breath The *last* however is frequently absent ... fear of death is more often present ... than in real anginas

In other cardiac disease a common source of diagnostic *error* arises from inefficient physical examination Thus congestive failure frequently ... because the size of the liver has not been investigated ...

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untreated than in the treated pregnant cardiac patient Adequate examination and evaluation of the cardiac status at the time of the patient s first visit proper selection of candidates for therapeutic abortion proper prenatal care in a special cardiac clinic sufficient bed rest and hospitalization digitalization when indicated and the proper method of delivery are the main factors responsible for the low maternal death rate in the treated group In such a regimen it is essential that every cardiac patient be examined during the first trimester when a therapeutic abortion is still feasible should such be indicated after evaluation of the cardiac status

Cesarean section has a limited although definite place in the treatment of heart disease in pregnancy In Stander s series the incidence of cesarean section on the indication of heart disease has been steadily declining during the past five years due no doubt to improved prenatal supervision and management as well as to a definite endeavor to register the cardiac patients in the special cardiac clinic as early as possible in pregnancy

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MISCELLANEOUS

Where We Fail in Diagnosis and Treatment of Heart Disease John A Oille[9] (Toronto) states that many diagnostic errors in cardiac disease are due to poor questioning e g in eliciting details of pain in the chest or arms When such a pain occurs its location duration character influencing factors and accompanying symptoms should be investigated In defining location inquiry should be made as to constancy and variability of the location of the pain in question and also as to presence of pain elsewhere in the body Brachial radiation has been incorrectly taken as evidence that the pain is cardiac neuritic pains of various origins have similar radiation The only diagnostic value of radia

[9] C d M A J 47 305 310 O t b 194

tion down the arms is that it excludes disease below the diaphragm Also while anginal pain may be located almost anywhere from the jaw to the eighth dorsal segment it is seldom situated in the axillary or submammary regions i e, between nipple and costal margins

Duration of pain is also of diagnostic significance Angina lasts roughly 1 30 minutes averaging about 3 Pains lasting hours or days are obviously not anginal Frequency is also important Thus, pains occurring daily for months or years are not due to coronary occlusion but may be due to spondylitis

Character of the pain may also give rise to error Variants include tightness fulness compression, etc Angina is a wave of pain never shooting or stabbing Angina does not change its character in the same patient, i e, it is never a sharp stab followed by a dull ache

The most important influencing factor in angina is exercise or excitement Angina results from myocardial anoxia and comes on during exertion not afterward The time factor is essential in production of anoxia in any muscle Therefore one must not be misled in a patient whose pain occurs from walking a block but not from walking up two flights of stairs Other factors which favor production of angina are a full stomach cold weather wind anxiety hurry and fatigue Apart from these considerations however there is a constancy about the degree of exercise which produces angina in the same patient In advanced cases the angina may come on when the patient is sitting or lying down

Accompanying symptoms in angina are sweating salivation urination and occasionally shortness of breath The last however is frequently absent The fear of death is more often present in cardiac neuroses than in real anginas

In other cardiac disease a common source of diagnostic error arises from inefficient physical examination Thus congestive failure is frequently overlooked because the size of the liver has not b

in absence of edema of the legs In right ventricular failure liver enlargement occurs earlier and more frequently than gravity edema Similarly presence of a mitral diastolic murmur may be unsuspected because the patient was not examined when lying on the left side

Error frequently arises from failure to perform necessary investigation A patient with suspected coronary occlusion should be kept in bed a week or longer with systematic recording of temperature white count and electrocardiograms A patient with chronic rheumatic endocarditis should be similarly investigated for signs of activity

Murmurs should be carefully assessed Any systolic murmur which can be made to disappear by standing breathing or exercise is unimportant A common misconception is that diastolic murmurs are inconstant This is not true of the murmurs of mitral stenosis In cases of severe failure or with any disease such as pneumonia which interferes with complete emptying of the left ventricle a mitral diastolic murmur may disappear Aortic diastolic murmurs practically never disappear

The Normal Heart and Conditions Simulating Cardiac Disease are discussed by E H Stokes[1] (Sydney) Since practically every symptom suggestive of cardiac disease may occur without detectable cardiac abnormality a positive diagnosis of a cardiac lesion should be made only in presence of indisputable findings In evaluating symptoms simulating cardiac disease Stokes reviewed findings in 15 normal individuals and in 45 others with simulative conditions (see Table p 556)

In determining the normality of the heart study of the patient s history should include consideration of habits activities previous health and medical history of relatives This should be followed by a comprehensive physical examination Stokes presents details of the cardiovascular examination

(1)—M J A t 1 2 53 263 S pt 19 194

Inspection —In a person with a normal heart, cyanosis, dyspnea orthopnea and dependent edema should not be present Prominence of the precordium may be present Position of the apex beat is an important indication of heart size It is situated in the fifth intercostal space usually not more than 4 in from the midline, this distance in the 15 normal students was 3 25-4 25 in A diffuse impulse does not necessarily indicate enlargement With tachycardia the apex beat may appear to be displaced but there may be no cardiac enlargement Re examination after disappearance of the tachycardia

Normal medical students		15
Conditions simulating cardiac disease—		
Anemia	1	
Emphysema	1	
Panniculitis	1	
Fibrositis	4	
Muscle sprain	2	
Pleurisy	1	
Pain of gastric distention	2	
Neurocirculatory asthenia	33	
	—	45
		—
Total		60

should decide the point Scoliosis pulmonary fibrosis pneumothorax or pleural effusion may all displace the apex beat

Palpation —This should confirm the position of the cardiac impulse noted by inspection The apex beat is the lowest and outermost point at which the examining finger is distinctly raised by each heart beat The apex beat may not be palpable when the chest wall is thick or when emphysema is present or more rarely when the heart is acting feebly During excitement a fine vibratory sensation may be felt but this differs in both time and intensity from the presystolic thrill of mitral stenosis comparable to the sensation produced when the hand is placed on the back of a purring cat

Percussion —In adults the normal area of cardiac dulness should not extend more than 4 ... to left or

1 75 in to the right of the midsternal line There may be a slight increase of these measurements in subjects whose hearts lie more than ordinarily in the trans verse position Percussion of the upper portion of the sternum over the aorta to exclude aortic dilatation or aneurysm is always desirable

Auscultation —This presents difficulties There are usually two heart sounds but a third is found in many healthy young adults If pronounced the third sound may be mistaken for an early diastolic rumble of mitral stenosis the so called opening click of mitral stenosis or reduplication of the second sound due to asynchronous closure of the aortic and pulmonary valves Usually however asynchronous closure causes reduplication of the second sound best heard at the pulmonary area while the normal third sound is most prominent at the apex or over the lower precordium Furthermore the interval between the two elements of a split second sound is not as prolonged as that be tween the normal second and third sounds The third sound and protodiastolic gallop cannot be distin guished by auscultation alone The latter however is usually associated with other signs of serious cardiac disease The first sound at the apex may be exag gerated by nervousness fever or exertion normally it is louder in young people than in older subjects The pulmonary second sound is usually louder than the aortic sound before 20 years but after 30 the aortic second sound is usually louder

Reduplication of either first or second sound may occur Reduplication of the first sound is uncommon it has been attributed to the impact of the heart against the chest wall and is said to disappear with recum bency Such reduplication differs from presystolic gal lop rhythm in its variability with change of position the relative softness of the first element in presystolic gallop rhythm and the fact that the latter is some times associated with bundle branch block Reduplica tion of the second sound is not uncommon especially

when the subject is observed during deep respiration

Murmurs are frequent in normal subjects An apical systolic murmur present during recumbency but absent when the patient is erect apparently has no pathologic significance, although some attribute it to slight mitral incompetence Similarly, a soft basal systolic murmur heard under like circumstances may generally be ignored especially if heard only in the pulmonary area

So called cardiorespiratory murmurs are frequently mistaken for evidence of organic disease They are usually heard only on inspiration and may be found at both apex and base of the heart

A harsh apical murmur constantly heard in both erect and supine positions and unaffected by respiration always suggests an organic lesion Owing to localization to a small area just medial to the apex beat the presystolic murmur is often missed In doubtful cases the subject should be asked to exercise his arms briskly and then assume a left decubitus position The typical presystolic crescendo murmur will then be heard if present Presence of a loud pulmonary second sound will be additional evidence suggestive of mitral stenosis

Anemia is a frequent source of systolic murmurs both apical and basal The bruits due to congenital heart disease may be mistaken for functional murmurs A loud hissing systolic murmur in the third and fourth left intercostal spaces near the sternum indicates a ventricular septal defect A systolic diastolic continuous machinery like murmur characterizes patent ductus arteriosus

Roentgen Examination—Fluoroscopy in the anteroposterior and right and left oblique positions aids in determination of size and shape of the heart and pulsations of its various chambers In estimating the size of the heart the cardiothoracic ratio is of value This is the ratio of the transverse diameter of the heart to the internal diameter of the chest East th

it should not exceed 1.2 In subjects with long narrow chests and hanging hearts it may be as much as 1 4 whereas in broad thick set individuals with trans versely situated hearts it may be as low as 1 19

Electrocardiography—Normal electrocardiograms are frequently misinterpreted Common sources of error arise from the effects of posture and respiration from digitalis administration and artefacts Master states that rotation of the heart rather than lateral move ment is the significant factor in alteration of electro cardiographic complexes Such changes may be marked including distinct axis deviation and even the appearance of a large Q wave in lead III and altera tions in the T wave Since these are usually interpreted as evidence of myocardial damage it is important to realize their possible benign origin White Chamber lain and Graybiel observed that inversion of the T waves in lead II although usually the result of heart disease or toxic states may be normal particularly in persons of asthenic habitus with vertical hearts and prone to neurocirculatory asthenia Position of the heart is the most important factor in producing this T wave inversion which is found in the sitting or stand ing position but is corrected by recumbency or by ele vating the diaphragm as at full expiration Autonomic nervous influences comprise another factor

The electrocardiogram is most valuable in elucida tion of the arrhythmias and management of coronary disease

Exercise Tolerance Tests—The first indication of car diac failure lies in diminished tolerance for exercise Of diagnostic value therefore are tests such as the following (1) walking briskly up 40 steps (2) 20 hops on the right foot and 20 on the left the shoulders being raised about 6 in at each hop (3) stepping off and on an 18 in chair 20 times Examination imme diately after the test should show no respiratory dis tress a pulse rise not over 10 to 20 beats per minute with resumption of the original rate in about a minute

when the subject is observed during deep respiration

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formed by fermentation Analyses have shown that it consists largely of nitrogen left from swallowed air Because nitrogen is not easily absorbed from the bowel nearly all of it contained in swallowed air must go on through to the rectum to be extruded as flatus Flatus does not contain much carbon dioxide or oxygen because these gases are easily and rapidly absorbed by the bowel and eliminated through the lungs From these considerations it is obvious that any condition which interferes with the return of venous blood from the intestine is likely to produce gaseous distention Pneumonia which interferes with the passage of gases from the lung can also produce intestinal distention As Fine has shown when an individual with a bloated abdomen is made to breathe pure oxygen there occurs a steepening of the gradient in nitrogen tension from the intestine through the blood to the pulmonary alveoli causing the gas to leave the distended bowel rapidly

Swallowed air usually is passed through a normal bowel easily rapidly and painlessly but gas resulting from the eating of some food to which the patient is sensitive often remains trapped for hours in painful tonically contracted bowel segments Relief comes only when perhaps with the taking of food waves again start traveling down the bowel

Often when an individual complains of gaseous distention roentgen examination of the abdomen will show that he is mistaken In adults there is usually little gas in the small bowel What gas there is in the abdomen is generally in the colon This may be due to the greater ability of the small bowel either to absorb gases or to pass them on rapidly Some of the gas in the intestine is apparently excreted from the blood Under the influence of emotion such excretion can occur with great rapidity

An isolated belch is usually due to a reverse wave coming up the esophagus from an overfull stomach but repeated belching is always due to air swallowing The swallowed air goes down only as far as the cardia and

Pulse —The two radial pulses should be examined with regard to volume tension, force, rhythm, rate and state of the vessel wall Blood pressure should also be recorded Retinoscopy may give important information regarding peripheral circulation

Conditions Simulating Cardiac Disease —These are numerous and varied The three principal symptoms suggesting organic disorder are breathlessness precordial pain and palpitation

Conditions causing breathlessness are anemia physical unfitness obesity, emphysema and other respiratory diseases such as pulmonary fibrosis latent pulmonary tuberculosis or pulmonary neoplasm

Certain conditions may cause pain which may be confused with that of heart disease Thus panniculitis, particularly in neurotic women may cause submammary pain on the left tenderness on pressure in the apical region is common The pain of intercostal fibrositis may simulate angina pectoris Sometimes fibrositis may affect the left pectoralis major muscle, and occasionally the pain is referred down the left arm Left pectoral muscle sprain is frequently misinterpreted as 'heart strain The pain of diaphragmatic pleurisy may be confusing but its relationship to respiration is distinctive Pain from a distended stomach may suggest angina pectoris but it is usually situated low and lacks characteristic radiation

Palpitation may result from premature contractions paroxysmal tachycardia paroxysmal auricular flutter and fibrillation Among extracardiac causes is tachycardia from emotional febrile or digestive disturbances that associated with thyrotoxicosis and that resulting from cardiac neurosis or neurocirculatory asthenia

What Causes Flatulence? Walter C Alvarez (Mayo Clinic) discusses the clinical aspects of flatulence and reviews the mechanisms of its production Contrary to the common impression most gas in the bowel is not

(1) J A M A 1 0 1 4 8 pt 5 194

bination of the three as is frequently the case suspicion is naturally directed to the gastro intestinal tract

Diagnosis of angina pectoris depends on a carefully taken and evaluated history The pain or discomfort is brought on by effort or emotion It may be less severe or absent if the patient walks when his stomach is empty or aggravated if he walks after eating a heavy meal The patient thus relates the pain to his digestive tract In addition pain may actually radiate to the epigastrium Nocturnal pain and gastric distress of coronary disease may result from overeating Nausea and vomiting in an elderly patient may be the only sign of coronary thrombosis of the silent type Care must be taken in evaluating nausea and vomiting when other gastro intestinal lesions are present for example carcinoma of the stomach ulcer and gallstones In these cases electrocardiograms especially serial ones are of decided value

Acute cardiac decompensation with sudden distention of the liver may simulate an upper abdominal emergency However other symptoms pointing to heart disease should be present With insidious congestive failure the gastro intestinal symptoms are less acute and have no constant characteristics Loss of appetite gas and vague abdominal distress may result If ascites develops bowel function becomes poor resulting in increasing gaseous distention anorexia and indigestion Embolism is one of the most frequently undiagnosed causes of acute gastro intestinal symptoms The pain may simulate gallbladder or renal colic or appendicitis Severe pain of sudden onset in a known cardiac patient should make the surgeon suspect the heart as the possible cause

Certain gastro intestinal lesions frequently cause symptoms that simulate heart disease Probably the foremost is diaphragmatic hernia which may produce substernal pain extending upward associated with dyspnea cyanosis and even shock thus simulating coronary infarction Acute dilatation of the heart after surgery may produce so much distress along with tachycardia

is then returned only occasionally is some forced into the stomach Repeated belching is generally an attempt to relieve a feeling of distress about the cardia and Alvarez considers that this distress is often due to reversed gastric peristaltic waves Ingestion of sodium bicarbonate may give relief by stopping such waves

Treatment for flatulence should not be instituted until it has been determined that excessive gas exists in the bowel The mechanism productive of such gas must also be ascertained Foods may be responsible in which instance elimination of roughage raw foods and some of the notoriously gas forming foods and laxatives may help sometimes relief is obtained by reducing the amount of food eaten Relief of constipation by enemas may give great relief

Some persons who wish to belch because they feel that they have gas in their stomach are relieved by sodium bicarbonate perhaps with some aromatic carminative added The value and mode of action of carminatives is doubtful Alcohol sometimes works well and peppermint is probably helpful In severe cases a teaspoonful of camphorated tincture of opium often works Walking is sometimes helpful because it starts the gas moving down the bowel Often the sipping of water or a little milk or the taking of a little food will help by starting waves running down the intestine When the gas starts to move out of the intestinal segment in which it has been trapped the pain is eliminated In some cases a diseased gallbladder must be removed and in others a failing heart must be rested

The Gastro Intestinal Symptoms of Heart Disease are discussed by Lewis M Hurxthal[3] (Lahey Clinic)

Congenital heart disease in infants may be associated with vomiting and malnutrition Aneurysm or other disease of the great vessels and rheumatic heart disease with mitral stenosis and auricular dilatation may cause dysphagia When the pain of coronary thrombosis is associated with gas nausea or vomiting or any com

(3) New England J Med 229 148 151 July 22 1943

the pulse easily and that a persistent rate of 120 or even 140 during a single and brief examination has little significance Much less has been said about bradycardia as slow rates are much more readily acceptable Present regulations state that a pulse rate of 50 or under is acceptable provided it is proved to be the natural pulse rate of the individual and yet heart rates around 40 per minute have been seriously questioned Evaluation of the pulse rate is difficult but White concludes from clinical observation that the normal pulse rate at rest or relative rest even in outstanding athletes has a tremendous range actually 35 118 per minute

The question as to blood pressure is harder Opinions differ as to the upper range particularly of the systolic level in a young man Although establishing a limit present regulations permit freedom of interpretation of that limit thus a cause for rejection is a persistent blood pressure at rest above 150 mm systolic or above 90 mm diastolic unless in the opinion of the examiner the increased blood pressure is due to psychic reaction and not secondary to renal or other systemic disease In evaluating blood pressure it must be remembered that most hypertensives of the future are probably among the present hyper reactors to excitement effort cold and drugs that their induction into the service with subsequent strain may in some instances accelerate or precipitate the process and that taxpayers will be penalized for years to pay for the disability of men whose hypertension may have developed in the service White considers that the upper limits of blood pressure readings during examination should not exceed 160/95

He believes that the following types of murmurs should be cause for rejection all diastolic murmurs all loud or moderate persistent systolic murmurs at the cardiac apex aortic valve area and the left lower sternal border and loud pulmonary systolic murmurs if persistent in all body positions and phases of respiration Acceptable murmurs are those which are physiologic and are principally pulmonary in location and systolic

dyspnea and even cyanosis as to lead one to suspect a pulmonary or cardiac complication Functional cardiac difficulties such as paroxysmal auricular fibrillation flutter and paroxysmal tachycardia are frequently associated with indigestion Premature systoles are a common complaint, more noticeable during indigestion but actually unrelated to any gastro intestinal disturbance Anemia from any cause may lead to cardiac symptoms

Gastro intestinal symptoms due to treatment are common and may be overlooked Digitalis is the most frequent offender but intolerance to such drugs as theobromine and ammonium chloride or even the mercurials may occur In the treatment of gastro intestinal symptoms in the cardiac patient drastic purges and saline cathartics are to be avoided. It is better to rely on a low roughage diet assisted by enemas of saline solution A soft solid diet that appeals to the appetite is advantageous

Gastro intestinal symptoms associated with heart disease are important because (1) they cause the patient to seek advice regarding his stomach and (2) they mislead even the physician Unnecessary x ray studies may be carried out on a patient whose cardiac condition cannot tolerate such procedures Recognition of the heart condition as the cause may save patients from dangerous surgical procedures Perhaps even more important is the recognition of gastro intestinal lesions causing symptoms of heart disease To diagnose heart disease without substantial evidence is inexcusable

Cardiac Problems in Wartime Paul D White[4] (Boston) discusses pulse rate blood pressure murmurs and neurocirculatory asthenia as they pertain to the armed forces At present Mobilization Regulations 1 9 state that a truly persistent heart rate of 100 or over should be considered cause for rejection Some examiners follow this recommendation literally but others believe that a rate of 120 at examination and even on repeated examinations is all right Lewis states that emotion raises

(4) Ann Int. Med 18 3 3 331 M h 1943

is suspected but the findings are equivocal demonstration of cardiac enlargement provides important evidence that organic heart disease exists (Fig 64) The teleroentgenogram is the most practical method for deter

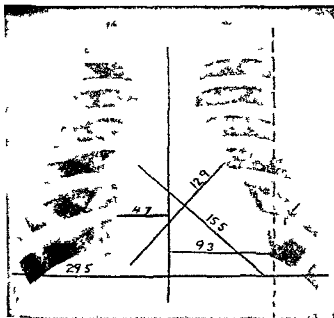


Fig 64—M 19 145 lb 6 ft 8 t ll H t ry d phy l e m t g t e pt fo blo d p e 158/56 ugg st ng t c in uffi cy ft yst l urmu t ba b t d t l mu m rt P d ct d t e se d m te (T D) f he rt i 12 3 m tu l T D 14 0 m wh h ceed p d ted f t l f 122 q cm by 28 p t Th e m m t d t d fi te d la g m nt C d tho t (T D f h rt)/(t rn l T D f he t) s rm l (47 per t) Th i th p t f ll d m em nt d h uld b d ded L ft h rt b d l n m d l (eul l d p t d fi t l ge m nt d m d l v ula and n ppl i (rrow) d t d

mining heart size Measurements are valuable to establish whether the size exceeds normal limits when it is not readily apparent whether the heart is normal or enlarged Two measurements suffice for such determination the transverse diameter and the area of the frontal cardiac silhouette related to prediction standards based

in time These vary with both body position and respiratory phase, being loudest when the patient is supine or during full expiration and become faint or tend to disappear at full inspiration or when the patient is upright Other murmurs that may be passed as normal are those produced in the lungs by the heart beat itself, i.e the sound of air currents and not of blood, and trivial or slight systolic murmurs at the apex, aortic area o over the lower sternum which tend to disappear like the louder pulmonary systolic murmurs with changing body position or respiratory phase It is important to remember that at least in adults who are not ill with anemia or acute infections apical and aortic systolic murmurs *are usually indicative of pathologic conditions in the* heart or aorta

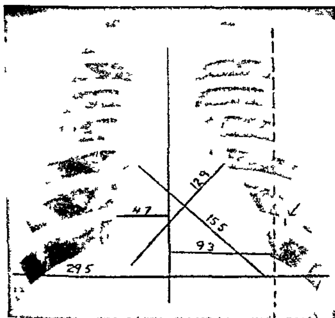
Neurocirculatory asthenia is a condition of ill health characterized by a group of symptoms consisting of dyspnea (often with sighing respiration), palpitation precordial pain or ache exhaustion, dizziness nervousness and sometimes tremor sweating, headache and syncope It is aggravated by effort or excitement and attends or follows infection or physical or nervous strain especially in 'hypersensitive individuals, who in extreme cases may show the condition more or less constantly with little or no provocation The task of eliminating actual or potential cases lies more in the province of the psychiatrist than in that of the cardiologist

Examination of the Heart in Navy Applicants H F Ungerleider T F Dubigg and R S Gubner[5] discuss the practical value of various signs and diagnostic procedures, with emphasis on signs which permit early recognition of organic heart disease rather than the classic signs associated with advanced stages

Cardiac enlargement is accepted as an unequivocal sign of organic heart disease Significant enlargement does not usually occur as an isolated finding, but in conjunction with other abnormalities such as elevation of blood pressure or valvular lesions When heart disease

(5) U S Nav M Bull 41 441 4 8 March 1943

is suspected but the findings are equivocal demonstration of cardiac enlargement provides important evidence that organic heart disease exists (Fig 64) The teleroentgenogram is the most practical method for deter



F g 64—M 19 145 lb 5 ft 8¾ t ll H tory d phy l min t n g t pt f bl d p u 158/56 gg st g rt uffi y ft y tol m mu at b b t n d t l murmu over rt P ed cted t se d m te (T D) f h art s 12 3 m tu l T D 14 0 m wh ch e ed p ed cted f ntal a f 1 q cm. by 28 p t Th m m t d t d fi t a d l g m t C d th ci t o (T D f h rt)/(t rn l T D f h t) rm l (47 per t) This a th poo t f ll d m u em nts d sh uld b d s ded Left h rt bo d l m d l l l n d p t d fi t l ge- m t d m d l ul d n pple h (arr w) d not co nc de

mining heart size Measurements are valuable to establish whether the size exceeds normal limits when it is not readily apparent whether the heart is normal or enlarged Two measurements suffice for such determination the transverse diameter and the area of the frontal cardiac silhouette related to prediction standards based

on weight and height The cardiac area may be calcu lated accurately from the product $\frac{\pi}{4}$ *long* $\times$ *broad* di ameters, obviating the need for planimetry A chart of nomograms has been prepared bv the authors indicating the cardiac area from the long and broad diameters and the predicted area from height and weight, together with the predicted transverse diameter from height and weight Use of the nomograms provides a convenient method for application of the transverse diameter and frontal area which are the most useful of the cardiac measurements Values exceeding 10 per cent above the predicted for either of these measurements are to be regarded as indicating that the heart is enlarged, since few normal subjects fall beyond this range

Analysis of Cardiac Abnormalities in 460 Selectees is presented by D E Markson and M P Gethner[6] (Chicago) Table 1 summarizes a group of 460 referred with questionable cardiac abnormalities Of these 117 were considered normal for they presented only minor variations of the normal sinus mechanism Essential hy pertension was found in 58 rheumatic heart disease in 137 neurocirculatory asthenia in 107 and other condi tions as listed in 41 It is significant that neurocircula tory asthenia made up about a third of the entire group Table 2 shows the reasons for rejection of 294 of the entire group Ninety three of these were classified as 1B and 201 as 4 unfit for service Thus 166 (36 per cent) of the 460 were considered fit for service

Standardization of these cardiac examinations was at tempted All diastolic murmurs whether heard at the apex or base were considered organic in origin and cause for rejection The systolic murmur heard in many healthy adults was considered significant only when in tensity was loud was increased by effort was heard after deep inspiration and after expiration and was present with change of posture In addition in obscure

(6) Ill ̶ o a M J 8 350 354 N ̶ mber 194

systolic murmurs electrocardiographic and radiographic studies were done and history was reviewed for rheumatic fever It was found however that repeated exam

TABLE 1

Total card ac cases referred from local boards			460
A M nor deviation from normal		11	[illegible]
Sinus arrhythmia—sinus tachycard a que t onable murmurs			
B Essential hypertens on		9	1[illegible]%
C Rheumat c heart d sease		137	0%
Mitral insuffic ency			
Mitral stenos s	34		
Aortic insufficiency	5		
Mitral and aortic insuffic ency	8		
Unclassified	18		
D Neurocirculatory asthenia		107	23%
E. Organic heart disease (not clearly classified)			
Cardiac hypertrophy	7		
Endocarditis	1		
Myocarditis	19		
Arrhythmias	9		
		36	8%
F Arter osclerotic hypertensive heart disease		2	
G Aur cular flutter		1	
H Aneurysm (Syphilitic)		1	
I Aortitis (Syphilit c)		1	1%
Total		460	

inations of the heart in questionable cases were definitely of more value in making final conclusions than was the electrocardiogram

TABLE .

Accepted	166	(36%)
Rejected	94	(64%)
Rejected 294—% of total rejected		
Essential hypertension	58	(20%)
Rheumatic heart disease	137	(46%)
N C A.	58	(20%)
Miscellaneous	41	(14%)
Classification of rejected inductees		
1B	93	(3[illegible]%) of total
4	01	(68%) of total

The presystolic crescendo murmur terminating in a snappy first tone was considered evidence of organic heart disease particularly when intensity increased after exercise This murmur was often confused with the

first tone occurring in the rapid heart of the apprehensive individual

Those with hypertension, whether transient or persistent with systolic pressure above 150 and diastolic above 90, were given a basal metabolic reading and an electrocardiogram and in some instances intravenous pyelography was done Re examinations were conducted two or three times to rule out the influence of fear on the blood pressure reading In no instance in this group was there evident renal pathology Basal metabolism alone could not be relied on to rule out hyperthyroidism and final decision depended on careful recheck of the individual under controlled conditions

Functional Heart Disease in Examination of Candidates for Naval Aviation is discussed by William Grady Mitchell[7] Cases of this type usually have been well studied and present no pathologic states Instead there is merely a systolic murmur usually apical but frequently at the base of the heart Nonorganic apical murmurs are usually due to a rapid excitable heart and are best heard after exercise with the patient in the left lateral decubitus position This murmur is commonly found in young people when after exercise or during excitement the blood is expelled with greater speed and force into the vessels Such murmurs are physiologic The other nonorganic and frequently heard murmurs are cardiorespiratory These are short inconstant and superficial They may only be heard with the patient in the prone position and during inspiration and are usually audible only over a relatively small area of the chest The effect of suspended breathing should be observed. Their relationship to respiration and their inconstancy are the outstanding characteristics

Systolic pulmonary murmurs are often heard They are best elicited with the patient supine and during expiration They are probably caused by a dynamic dilatation—physiologic—of the pulmonary artery They are physiologic

(7) U S N v M Bull 40 834 839 Oct ber

The rubbing together of uninflamed pericardial and pleural surfaces may also cause murmurs which usually disappear when the breath is held in expiration The relative constancy and quality distinguish organic from functional and accidental murmurs The organic murmur is usually louder harsher and constantly present It is also heard as a rule in all positions It may be better brought out and identified by exercise This is noteworthy in mitral stenosis where the presystolic element becomes more audible or the first heart sound more snapping in quality Location of the murmur timing tonal characteristics and associated findings make the case clear

Presence of such physiologic murmurs does not disqualify an individual for aviation training However certain benign arrhythmias such as ventricular premature contractions call for rejection because of their tendency under stress and nervous tension to pass into a more serious cardiac state

The Schneider Index as Modified by Diseases of the Circulation is discussed by Harold Feil Mechael Petti and Olive Park[8] (Western Reserve Univ) The index is based on six sets of observations (1) pulse rate in the reclining position (2) standing pulse rate (3) increase in pulse rate when standing and recumbent rates are compared (4) increase in pulse rate after standard exercise (stepping on a chair 18 in high five times) (5) time required for the heart rate to return to the standing rate after exercise and (6) change in systolic blood pressure when the examinee stands *A slow pulse* initially a slight increase in pulse rate on standing and after exercise a quick fall in pulse rate after exercising and a rise in systolic blood pressure on standing raises the index

The test may be used both for screening and for periodic check up Conclusions must not be drawn from the test alone without evaluating all other methods of examination Service regulations state that a low index

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alone is insufficient for disqualification Scoring is lowered by previous exercise, emotion infection excesses of any sort and physical deficiencies Ingestion of food fatigue and careless testing affect the score

The test must be carefully done Subject and examiner must be alone in a quiet room Preliminary rest must be provided on a comfortable couch Due consideration to the ingestion of food or liquor smoking, recent illness emotion and fatigue must be given The examiner must appreciate that any test when taken for the first time may be poorly performed even by subjects in excellent condition because of emotional influences

As the Schneider test is widely used in examination of aviation recruits it is important to re emphasize its limitations To ascertain these limitations the authors applied the test to 138 young normal adults and to 126 patients 121 of whom had serious cardiac or hypertensive disease Those in the latter group frequently showed favorable Schneider indexes thereby indicating that the test cannot be used to differentiate normal from abnormal cardiovascular states The test is most valuable for follow up observations for a lowering of the index signifies some variation in either the psychic or the physical condition

Shock Physiologic and Clinical Aspects Earle B Mahoney and Joe W Howland[9] (Univ of Rochester) discuss treatment of shock This may be divided into two main categories (1) general features including oxygen and drug therapy and (2) fluid replacement

General Features—The patient should be made as comfortable as possible and small doses of morphine are not contraindicated after the extent of injury has been determined Major bleeding should be controlled and compound fractures should be temporarily immobilized to prevent further damage to soft tissues It is advisabl to conserve body heat by means of blankets etc but excessive external heat is contraindicated The shock position should be instituted Administration of a high

(9) Surgery 13 188 198 February 1943

concentration of oxygen is of value in combating the anoxemia which is one of the dangers of shock

Use of vasopressor drugs such as adrenalin and ephedrine should be discouraged for it has been shown that shock may be produced by prolonged administration of adrenalin Only in early neurogenic shock are small amounts of ephedrine or adrenalin permissible Adrenal cortical extract is being recommended in shock on the theory that it will prevent or decrease capillary permeability Its administration is logical if there is a generalized increase in capillary permeability in secondary shock if all the fluid is lost at the site of the damaged capillaries it would seem of less value

Fluid Replacement —The most fundamental aspect of shock treatment is replacement of the various elements lost from the circulation Proper treatment demands an understanding of the relative proportion of red cells fluid and protein which are lost in various types of hematogenic shock Figure 65 is a schematic representation of the relative amounts of the three elements present in the blood stream when the decreased blood pressure is due to (1) dehydration (2) hemorrhage (3) trauma and (4) burns Electrolytes and other plasma constituents are disregarded for purposes of simplicity The dehydrated patient requires only the parenteral injection of normal saline solution The total circulating protein and red cells have not been depleted

When the blood volume is depleted by hemorrhage the protein fluid and red cells are lost in the same proportion as they existed in the blood If hemorrhage has been minor the volume may be restored with saline solution or if more extensive whole blood should be used The body will tolerate extensive loss of red cells but extensive hemorrhage may result in serious protein loss If the circulation is restored with plasma red cells may be mobilized from areas of stagnation or reserve sources Brennan has shown that an actual increase in circulating red cells may result from plasma injections following hemorrhage Slow prolonged hemorrhage may

result in the visceral changes of traumatic shock and will consequently require the same type of treatment

In traumatic shock whole blood is lost at the site of injury but there is an excessive loss of plasma from the damaged capillaries Consequently, the total red cell volume may be decreased but the most marked decrease occurs in the fluid and protein elements of the circulation Actual determinations of plasma volume may indicate a 50 per cent reduction of fluid Although the concentration of circulating plasma protein may be

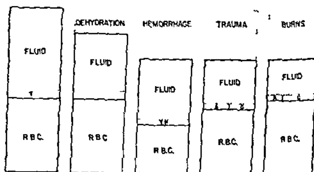


Fig 65 — Shift f blood omponent in sho k

normal or only slightly decreased the total circulating protein is greatly reduced Intravenous injection of saline solution is detrimental for it causes dilution of the remaining protein and a resultant decrease in colloid osmotic pressure It may cause a temporary increase in blood pressure but the increased hydrostatic pressure will result in further protein loss and more profound shock Plasma or whole blood should be used in traumatic shock to replace adequately the depleted circulation The large amounts necessary must be emphasized as 1 500 2 000 cc is often required for an adult

Shock resulting from burns is almost entirely due to plasma loss in the vesicles of the burn and in the underlying tissues The red cell volume remains essentially unchanged and the hematocrit incr

is greatly reduced and a tremendous amount of plasma protein is lost The fluid in the vesicles contains 4 5 Gm per cent of protein and since about 90 per cent of this is albumin an inversion of the albumin globulin ratio results It is of interest to note that in recently burned patients the protein loss is so great that the plasma specific gravity and protein concentration decreases The burned patient therefore requires large amounts of plasma to replenish the fluid and protein Saline injections are as deleterious in burns as in traumatic shock because of protein dilution and resultant edema

Shock Its Dynamics Recognition and Management Virgil H Moon[1] (Jefferson Med College) states that final agreement on the mechanism of shock has been delayed by confusion due to several causes The first was incomplete understanding of the functions and reactions of capillary endothelium which is easily affected by various noxious agents and conditions

Any type of injury to endothelium increases its permeability to plasma colloids Abnormal permeability of endothelium disturbs seriously the mechanism of water balance Leakage of plasma from the blood produces hemoconcentration lowers the total blood volume and leads to disparity between it and the volume capacity of the vascular bed This disparity if uncompensated manifests itself in the characteristic signs of shock

A second cause was that many surgeons and others consider surgical or traumatic shock a separate entity and have not recognized its fundamental kinship to the same type of circulatory deficiency which occurs under other conditions of disease

A third cause has been failure to distinguish between shock and effects of hemorrhage Several of the clinical signs of shock and hemorrhage are identical but other accompanying features are opposite in character In shock the capillary endothelium becomes permeable vomiting and diarrhea are frequent infusions of fluid

(1) C ti J M d 4 588 595 F bru ry 1943

or transfusions of blood are often ineffective, nonprotein nitrogen, potassium, calcium and magnesium contents of the blood are markedly increased, sodium chlorides and carbonates are decreased, the coagulation time is lengthened and the sedimentation rate retarded and the urine is decreased in volume and contains albumin erythrocytes casts bile and other abnormal substances Autopsy findings include edema, serous effusions capillovenous congestion, stasis and petechiae in the viscera atony of the gastro intestinal tract focal necroses and acute degeneration of parenchymatous organs None of these features result from simple hemorrhage Hemorrhage *when present, is an important contributory factor to shock* but distinctions between the accompanying physiologic disturbances invalidate the assumption that shock and the effects of hemorrhage are *identical*

Factors of error inherent in experimental methods constitute another major source for confusion A method commonly used is to narcotize an animal deeply and to produce extensive trauma to the tissues accepting a decline in blood pressure as the indicator of shock This method is open to serious objections as the result may be due to the narcotic to absorption of products from traumatized tissues to the associated hemorrhages or in part to each However methods devised for testing the effects of absorption uncomplicated by anesthesia and *hemorrhage showed that absorption is a factor in producing circulatory failure*

Finally the belief that shock is purely a physiologic disturbance unaccompanied by significant morphologic features hindered the clarification of the problem

The principles on which management of shock is based are simple and logical The best treatment is *prevention* Early débridement of lacerated wounds local treatment of burns by coagulation surgical relief of an infarcted or strangulated loop of bowel and drainage of extensive areas of infection are important measures *The first* essential in treatment is an accurate differential

diagnosis between three conditions which commonly re sult from wounds and present similar clinical features primary or initial shock effects of hemorrhage and true or secondary shock

Hemoconcentration is most valuable for differen tiation Whatever method is used a reading should be made when the patient is first seen Subsequent read ings at intervals of one or two hours will indicate the degree and progress of the condition whether shock or hemorrhage affects the circulation

Primary shock has essentially the same origin and mechanism as fainting or syncope It develops imme diately after injury is usually transient and requires no other treatment than quiet and rest in a horizontal position It does not produce concentration of blood The lapse of time between injury and circulatory dis turbance and the presence or absence of hemoconcen tration are the most valuable points of distinction be tween primary and secondary shock

Severe hemorrhage may cause clinical signs exactly like those of secondary shock They are differentiated by the fact that hemodilution occurs immediately after hemorrhages and the degree of dilution is proportional to the amount of blood lost

Secondary shock requires several hours for develop ment It is seldom seen within four hours except in ab dominal or cranial injuries Marked decline in the ar terial blood pressure has been overemphasized as a cardinal feature The incipient stage of shock may be de tected by moderate hemoconcentration 10 20 per cent even before any evidence of circulatory deficiency is manifested clinically This finding serves to distinguish it from primary shock or from the effects of hemor rhage

Stimulants such as adrenalin strychnine and digitalis are useless and occasionally distinctly harmful The use ful remedies are those agents which tend to counteract anoxia endothelial permeability and reduced blood volume

Inhalation of oxygen aids in counteracting anoxia and preventing irreparable damage raises metabolic activity and tends to interrupt the vicious circle even after shock has been initiated Adrenal cortical hormone maintains the normal impermeability of endothelium and is distinctly beneficial in prevention and treatment of shock Fluid replacement to restore blood volume to an adequate level is highly important This fluid should approximate closely the composition of that lost, thus. after serious hemorrhages transfusions of whole blood provide the ideal remedy In shock accompanied by hemoconcentration the best replacement fluid is human plasma or serum Plasma concentrated to one half or even one fifth its original volume is even more effective in counteracting both the low blood volume and the deranged equilibrium of fluids which are prominent factors in the mechanism by which shock develops Use of acacia is advised only when neither plasma nor serum is obtainable

Range of the Normal Heart in Athletes According to J W Wilce[3] (Ohio State Univ) many athletes who should furnish some of the best general military, officer and aviation pilot material are being legitimately rejected from *service for cardiac conditions* Although broad participation in competitive athletics is a characteristic part of American life there is still a great deal to be learned concerning the cardiac effects of athletics Lewis states that burdens imposed by physiologic acts on the normal heart however heavy never injure heart fibers never produce injurious dilatations *and never exhaust the heart s reserve*

Wilce reports on a 13 year study of the history and cardiac size of 233 male American athletes aged 16 80 made to obtain evidence concerning the following postulates (1) Athletic heart in the sense of a permanently enlarged clinically inferior heart does not exist in the absence of etiologic factors which are scientifically accepted as the cause of actual or potential cardiac dis

(3) Am H a t J 25 613 630 May 194?

ease (2) Certain so-called normal hearts may show relatively minor transitory physiologic changes which have little if any practical clinical significance

Contrary to the popular belief that the heart enlarges under conditions of work or exercise Wilce found in his series that some hearts are enlarged some are normal and some are small The absolute enlargements which would be called athletic hearts by some may be explained by inheritance disease or deficiency factors before during or after active sport The usual normal constitutional variations in heart shape are naturally also normal for adults

Strictly speaking a normal healthy heart is one which shows no evidence of organic disease congenital or acquired no abnormal variations in size or shape under accepted standards no evidence of deficiency or degenerative conditions no abnormal variation in functional efficiency and no history of any condition which is known to predispose to heart disease or to favor it In Wilce s series only 29 hearts were normal If no abnormal variation in size or shape under accepted standards is omitted 37 were normal On the basis of evidence available in these 37 athletes athletics is postulated as the only possible influence on heart size Seven of these 37 hearts postulated as normal were therefore enlarged by athletic competition and would qualify as true athletic or work hearts or normal hearts physiologically enlarged by exercise

With regard to physiologic changes in the heart size examination of two athletes showed increases in the size of the heart over a period of several years but in neither case was the heart absolutely enlarged

This study reveals definitely that there are many injured hearts among athletes before during and after competition This may explain military rejections of athletes popularly considered normal The tendency for the layman is to consider these rejections due to athletic heart Such is not the case as they were rejected because of organic heart disease of varying degree

Wilce concludes that 'nonorganic cardiac enlargement" is probably of little clinical importance and should be considered *normal for athletes* Moderate variations from the average heart size in normal athletes, in the absence of other signs of organic heart disease, is of no particular *significance* The eventual result of "nonorganic enlargement" however is not yet definitely known

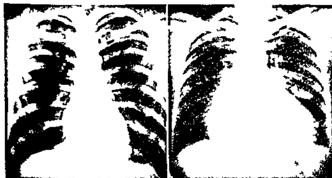
The *intangible advantages of true athletic training* probably outweigh the disadvantages of moderate, 'nonorganic cardiac enlargement' (granting that such does exist), this is important in deciding whether or not athletes are acceptable for aviation or other military service Such hearts should be considered normal.

The Importance of the Cardiac Impulse in Determining the Size of the Heart is discussed by H L Smith[4] The normal cardiac impulse is an outward and inward movement of a small portion of the thoracic wall between the ribs just to the right of and below the left nipple It is produced by impact of a portion of the right ventricle against the thoracic wall On most normal adults this impulse is seen in the fifth interspace just to the right of the nipple line slightly to the right of the midclavicular line and 7 9 cm from the midsternal line although occasionally it is observed in the fourth or sixth interspace On normal children it is often higher than the fifth interspace and to the left of the midclavicular line The position of the impulse varies somewhat with changes of body position It shifts slightly, depending on which side the patient lies on and is more prominent when the patient is upright than when recumbent Some change also occurs with forced inspiration and expiration Some normal individuals in addition to the outward thrust of a localized portion of the thoracic wall have an outward thrust of a rather large portion of the thoracic wall This is noted especially after exercise in persons with a thin thorax

Palpation usually confirms information obtained by

(4) Proc. Staff Meet., M yo Cl n. 18 77 80 Ma 10 1943

inspection and often gives added information Features to be noted in studying the apex beat are its site and character i e whether it is a slow forceful thrust a short weak tap or a diffuse weak slap against a wide region of the thoracic wall When the heart is weak hypertrophied and dilated the striking of both ventricles against the thoracic wall can often be demon



F g 66 (l ft) —Sm ll p f l d pl ed d mp l e n fifth i tersp f p t t w th h rt f m l iz

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strated Patients with congestive heart failure often present a visible cardiac impulse 10 13 cm in diameter during treatment decrease in this area can be noted daily

For practical purposes the maximal cardiac impulse indicates the site of the left heart border Smith has demonstrated this roentgenologically in many normal persons and in patients with cardiac hypertrophy (Figs 66 and 67) In practically all with enlarged hearts and in most normal individuals the impulse site corresponded closely to the left heart border

Gallop Rhythm Incidence and Influence of Age Race and Sex Gallop rhythm is characterized by the occurrence of three heart sounds during each cardiac

cycle Systolic gallop is rare and apparently not of much clinical importance, while diastolic gallop is of great clinical significance Curtis F Garvin[5] (Western Reserve Univ) presents data on this type obtained *from the clinical and pathologic records of 790 consecu* tive adults who died of heart disease Gallop rhythm had been present in 199 and seemed to be due mostly to auricular contraction In only two patients was auricular

FREQUENCY DISTRIBUTION OF GALLOP RHYTHM IN VARIOUS TYPES OF HEART DISEASE

TYPE OF HEART DISEASE	NO OF CASES	WITH GALLOP RHYTHM NO	%
Hypertensive heart disease	264	93	35
Coronary heart disease	177	55	1 1
Rheumatic heart disease	119	12	10 1
Syphilitic heart disease	67	7	10 4
Cor pulmonale	54	10	18 [illegible]
Subacute bacterial endocarditis	31	2	6 4
Acute bacterial endocarditis	13	1	7 7
Thyroid heart disease	9	1	11 1
Calcific aortic stenosis	9	3	33 3
Obliterative pericarditis	7	0	0 0
Tuberculous pericarditis	7	4	[illegible]7 1
Miscellaneous	14	3	1 4
Undiagnosed	19	8	4[illegible] 1
	790	199	5[illegible]

fibrillation present and the gallop presumably was due to a third heart sound No doubt this was the etiologic factor in a few more instances although such cases ap peared to be in the minority

The incidence of gallop rhythm in the various types of heart disease is shown in the table One out of every three patients with hypertensive heart disease and coronary artery disease had this type of rhythm *Cor pulmonale* was *associated with it in about one case in* five Only 1 of 10 patients who died of rheumatic or syphilitic heart disease had gallop rhythm

It is generally thought that gallop rhythm may read ily occur in patients with active rheumatic carditis but that it is extremely rare in patients with well developed mitral stenosis This idea is supported by the study

(5) Am J M S 205 814 819 June 1943

In the other common type of valvular heart disease (syphilitic) gallop rhythm likewise is considered to occur uncommonly Of the 67 persons who died of syphi litic heart disease 7 had gallop rhythm and in only 4 was there apparently no other explanation for the gal lop than the syphilitic heart disease

Average age at death of 93 patients with hypertensive heart disease and gallop rhythm was 49 5 years of 171 patients with hypertensive heart disease and no gallop rhythm 58 8 years Fifty five patients with coronary artery disease and gallop rhythm averaged 57 3 years at death and 122 with coronary heart disease and no gallop rhythm 64 4 years Both these differences seem to be statistically highly significant Even if patients with auricular fibrillation are excluded (such patients rarely have gallop rhythm and are apt to be older) it still appears that the average age at death of cardiac patients with gallop rhythm is less than the average age of cardiac patients without gallop rhythm

If the patients with hypertensive and/or coronary heart disease are grouped together of 326 white pa tients 100 had a gallop while of the 115 Negro pa tients 48 had a gallop This seems to indicate that Negroes with fatal hypertensive heart disease and/or coronary heart disease show a higher incidence of gallop rhythm than white patients It is thought that this is really a manifestation of the influence of age for the average age at death of the Negro patients was less than that of the white patients

No association between gallop rhythm and sex was demonstrable

Clinical Significance of Loud Aortic and Apical Systolic Heart Murmurs Lyle A Baker Howard B Sprague and Paul D White[7] report results of a follow up study on patients first seen 10 or more years pre viously Only those were studied who presented loud systolic murmurs heard best at either the aortic or the apical area without a diastolic murmur being present

(7) Am J M S 206 31 43 J ly 1943

Satisfactory information was obtained on 187 of 2/3 patients investigated Of these, 124 had heart disease of the degenerative type (coronary arteriosclerosis, hypertension or both) Average age when they were first seen was 64 Forty were placed in the rheumatic group Average age at first examination was 35 In 20 patients the etiology of the heart disease was uncertain, but in most instances it was probably rheumatic Two patients had congenital heart disease and one syphilitic heart disease

Of the 187 patients 155 had died at the time of the follow up study In 142 the cause of death was known it being cardiovascular disease in 92 2 per cent In 85 9 per cent death was directly cardiac in nature The fact that cardiac deaths occurred in such a high percentage of patients with loud systolic murmurs indicates the prevalence of serious heart disease among these persons The mortality in each etiologic group and the total mortality for 10 year and 15 year periods are given in the table The authors believe that there are several reasons for the marked difference in mortality between degenerative and rheumatic types of heart disease The course of the former is usually shorter The average age of those with rheumatic heart disease was nearly 30 years less than that of the degenerative group A more important reason is that loud systolic murmurs in the apical region in persons with degenerative heart disease are due to relative mitral insufficiency cardiac hypertrophy and dilatation being more frequent and more marked

In this series the 10 year expectancy of females was definitely better than that for males By the end of 15 years this difference had disappeared A normal heart size appears to justify a better prognosis than an enlarged heart this being particularly true if the heart disease is of rheumatic etiology Forty eight per cent of the deaths occurred within a year after the first examination while 71 per cent occurred within three years When the total number of cases in each group

is considered there is no appreciable difference in mortality between degenerative and rheumatic types of heart disease during the first year Masking of the first heart sound at the point of maximum intensity of the murmur was noted in only one patient still alive while it was not uncommon in those with apical murmurs who died Despite these prognostic trends however it is impossible to predict with any degree of assurance the course in any particular case

MORTALITY AFTER 10 AND 15 YEAR INTERVALS ACCORDING TO ETIOLOGY

GROUP	FOLLOW UP INTERVAL, YR	PATIENTS FOLLOWED	LIVING	DEAD	MORTALITY %
Degenerative	10	124	19	105 (14)	84 6
	15	119	2	117 (16)	98 3
Rheumatic	10	40	21	19 (3)	47 5
	15	33	8	25 (4)	75 7
Uncertain cause	10	20	10	10	50 0
	15	15	3	12	80 0
Congenital	10	2	1	1	50 0
	15	1	0	1	100 0
Syphilitic	10	1	1	0	0 0
	15	0	0	0	0 0
Total	10	187	5	135	72 1
	15	168	13	155	92 0

Number in p nthe nd to tho e who died of no ca d u

Some patients originally thought to have mitral regurgitation because of a loud apical systolic murmur were later found to have aortic stenosis which in the course of 10 or 15 years tended to precipitate abrupt left ventricular failure (acute pulmonary edema) The clue to these cases lies in the fact that the loud somewhat harsh systolic murmur heard at the apex is also heard at the aortic valve area although perhaps less loudly The murmur is primarily an aortic systolic murmur well

Satisfactory information was obtained on 187 of 273 patients *investigated*. *Of these*, 124 had *heart disease* of the degenerative type (coronary arteriosclerosis hypertension or both). Average age when they were first seen was 64. Forty were placed in the rheumatic group. Average age at first examination was 35. In 20 patients the etiology of the heart disease was uncertain but in most instances it was probably rheumatic. Two patients had congenital heart disease and one syphilitic heart disease.

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prostatic resection has reduced by 90 per cent the imme diate postoperative mortality rate formerly encountered in suprapubic and perineal prostatectomies

The authors review 29 cases with a history of active myocardial failure or of recent myocardial infarction in which operation for the urologic condition was recom mended As a whole they were cases in which surgery is often not advised Ages varied from 55 to 83 (aver age 71) Seven patients have died a percentage of 24 1 *After taking into consideration the various complica* tions it can be said that only two of these patients who had signs of circulatory failure prior to admission be came worse immediately after operation and one of these had had bronchiectasis for a number of years This makes the percentage 6 8 All the patients belonged to the class who undoubtedly would have died early of circulatory failure had not surgical intervention been done

Hypertension was present in eight patients prior to operation and on discharge pressure was within normal limits Average hospital stay before any surgical pro cedure was 11 5 days average postoperative stay 10 4 days and average total hospitalization 21 9 days Four patients had suprapubic prostatectomy and two supra pubic prostatectomy following resection the others had resection

In only four cases were laboratory data indicative of nitrogen retention so that it can be eliminated as a cause of failing circulation An important seldom men tioned factor is the strain associated with frequency and marked exertion during urination This straining must be a *definite factor in circulatory failure because* cys totomy or an indwelling catheter will usually bring on more or less relief to the heart muscle Bed rest was not necessary for cardiac improvement as many of the pa tients were not confined absolutely to bed All except those mentioned showed great improvement following operation

The choice of a proper anesthetic is of importance

transmitted to the apex as well as into the neck vessels a mitral regurgitant *murmur is often* well heard at the lung bases (and in the axilla) but not at the aortic valve area

A general acceptance by the profession of the unimportance of systolic murmurs makes it necessary for those interested in heart disease to attempt a clarification of the issue It is evident from the authors results that loud systolic murmurs at the cardiac apex or aortic valve area are clinically important even in the absence of diastolic *murmurs* and of well marked cardiac enlargement

Circulatory Disturbances in Prostatic Hypertrophy Meredith Mallory Fred Mathers Louis M Orr II, and Palmer R Kundert[9] (Orlando Fla) state that there is little in the literature on the important relationship of the hypertrophied prostate to circulatory disturbances. Most diagnosticians still consider the patient with the cardiovascular renal syndrome a poor surgical risk and there is a general tendency to treat prostatic hypertrophy too conservatively because of the presence of some degree of circulatory failure The final decision as to surgery is left by *many urologists to the internist* or cardiologist and too often the opinion is that the patient is not able to undergo operation He is allowed to die *rather than to be submitted to the risk of removal of the obstruction* which in practically *all cases* would help to improve the circulation

The inter relationship between renal dysfunction and cardiac impairment has been clearly demonstrated by Thompson in a *large series of patients subjected to* prostatic surgery at the Mayo Clinic Preoperative strengthening of the myocardial reserve is the essential step in lessening the hazards of major surgery and the preoperative period must not be curtailed or hurried Elevation of *blood* pressure *should* not *be a contraindication* to surgery Mortality rates vary with the experience of the operator and it is claimed that transurethral

(9) Ann Int M J 18 835 840 May 1943

there were both a history and definite physical findings of rheumatic heart disease All presented auricular fibrillation which caused emboli to be thrown from the left auricle to the aortic bifurcation Emboli were thrown off to other arteries in six of the cases

'Thrombo arteriosclerosis of the aorta is used to indicate the underlying process of atheromatous degeneration and ulceration with superimposed thrombus formation Five cases were in this category The ages ranged from 50 to 80 (average 62) There was only one woman in this group In one case a postoperative thrombocythemia was a secondary factor in deposition of a thrombus

In one case (woman 84) autopsy showed an arteriosclerotic aneurysm just above the aortic bifurcation In another case with a normal aorta and heart bilateral iliopsoas abscesses secondary to a sarcoma resulted in formation of septic thromboses of capillaries in the periaortic tissues This gave rise directly to an adherent thrombus The aorta was not invaded by the malignancy

Twelve of the 16 cases were diagnosed ante mortem Temperature and color changes were present in all The color changes were variously described as black cyanotic mottled blanched blue pale or white the temperature changes as cold and clammy Rarely was superficial gangrene or bleb formation noted The typical symptoms of severe sudden pains in the extremities occurred in 11 cases The pain at times radiated into the lower back inguinal regions or girdle area and varied from slight to severe Varying degrees of shock ensued four times Pulsations were absent in nine patients Weakness of the extremities loss of sensation and absent reflexes were other common findings

A correct diagnosis was not made in four cases because of complete absence of signs or symptoms pointing to occlusion of the aorta or blood supply of the extremities There was insufficient time for visible changes to develop in the extremities before death ensued in shock or coma One patient presented symptoms of vomiting

Pentothal sodium given in conjunction with oxygen most clearly satisfies the requirements of the cardiac case

Infusions of plasma or whole blood should be part of the routine postoperative treatment in severe cases Loss of blood will probably average 300-400 cc

Cardiovascular Allergy Hal M Davison James C Thoroughman and Harold Bowcock[1] (Atlanta, Ga) summarize a number of representative articles on various forms of cardiovascular allergy These articles show that anaphylactic and allergic processes in some cases have caused demonstrable pathology in all of the blood vessels including those of the heart, and also in the tissues of the heart No typical demonstrable changes in the heart and blood vessels occur in uncomplicated bronchial asthma Periarteritis nodosa and thrombo angiitis most often occur in hypersensitive individuals and are probably allergic in origin In certain patients attacks of angina tachycardia or ventricular extrasystoles can be produced at will by heat cold and effort These attacks can be terminated by use of the opposite medium or use of epinephrine There is a relationship between allergy and some cases of hypertension and of nephritis There is in some instances a relationship between allergy and certain manifestations of cardiac abnormality such as extrasystoles tachycardia paroxysmal tachycardia angina and coronary occlusion

The authors give a résumé of 15 cases all showing one or more allergic phenomena and presenting cardiac symptoms such as tachycardia paroxysmal tachycardia auricular fibrillation or auricular flutter In one case, paroxysmal tachycardia was repeatedly produced by the ingestion of milk

Occlusions of the Abdominal Aorta Study of 16 Cases of Saddle Embolus and Thrombosis was made by Nathaniel F Reich (Kings County Hosp Brooklyn) Included in the group are seven cases of embolism, all in women aged 32 61 (average 43) Without exception

(1) South M J 36 560 567 August, 1943
( ) Ann Int Med 19 36 59 July 1943

travascular tension suggests the importance of high arterial pressure in the causation of this condition

Thrombo angiitis obliterans etiologically remains a mystery Its predilection for males young adults Jews and tobacco smokers is generally recognized but unexplained Its course is extremely variable and its distribution patchy There is no indication that any single preventive or therapeutic measure is specific

Raynaud s disease is thought to be due to an abnormal vasoconstrictor response to local cold or to a hyper reactivity of the sympathetic nervous system However its frequent association with certain other diseases suggests that in many cases it is merely a local manifestation of a more serious systemic disorder

Periarteritis (polyarteritis) nodosa is essentially a fibrinoid necrosis of the arterial wall with an associated acute subacute or healing inflammatory cellular reaction that also involves the perivascular tissues Its frequent association with asthma urticaria and eosinophilia suggests a hypersensitive background Some observations arouse speculation whether the increasing incidence of periarteritis may be due to the increasing use of serums vaccines and sulfonamides

The ischemia caused by arterial occlusion is probably the most potent stimulus for promotion of collateral circulation which in turn is the most important factor in determining the ultimate effects of an arterial occlusion These facts are still little appreciated judging from the great variety of therapeutic measures reported to be of more or less specific value in treatment of occlusive arterial disease

Intermittent venous occlusion is claimed to be beneficial because it may be followed by reactive hyperemia and because it has been reported to produce an increase in arterial blood flow during the obstruction period However it has recently been shown in man and animals that venous obstruction decreases arterial blood flow during the period when venous pressure is increased (above about 30 mm Hg) Other observations have in

and right upper quadrant pain and tenderness Another patient with bronchiectasis suddenly died and autopsy revealed acute occlusion of the abdominal aorta The fourth patient had fecal vomiting and a mass in the left lower quadrant

Following onset of acute symptoms, duration of life ranged from 6 hours to 1 month (average 10 days) None of the patients was subjected to embolectomy since most of them applied for treatment too late or after gangrene became apparent In others the general condition precluded surgery Two patients in the series recovered The oscillation bed was used with favorable results in one of these This patient was also given large doses of vasodilators (papaverine aminophylline whisky) as well as digitalis Later ultrashort wave therapy was used Recovery occurred two months after treatment was started Reich suggests that heparin might be of value in such cases to mitigate a progressive occlusion

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THE PERIPHERAL BLOOD VESSELS

Peripheral Vascular Disease Robert W Wilkins and Carl K Friedland[7] (Boston Univ) state that atherosclerosis is the most prevalent vascular disease of adults It is due to a selective invasion of the arterial intima by cholesterol laden (foam) cells derived from the reticulo endothelial system Following the breakdown of these cells de esterified cholesterol is deposited in the subintima as plaques which act as foreign bodies Vascularization fibrosis and calcification of such plaques occur in varying degrees to produce the familiar lesions of atherosclerosis Hereditary predisposition must be of great significance in determining the occurrence of the disease The fact that various hypercholesteremic disorders are so frequently complicated by atherosclerosis indicates that a derangement of lipoid metabolism plays a fundamental part in its etiology The greater frequency of atherosclerosis in arteries under increased in

(7) New England J Med 29 16 July 1 ....

feet and lower legs have been swollen and anesthetic almost to the knees and the distal halves of the feet have appeared gangrenous Low grade fever is not un common for the first few days after rescue and is no cause for alarm

After warming of the body the limbs become hyper emic and remain so for several days to six weeks The hyperemia is associated with an increase in edema formation and occasionally with the appearance of blebs containing serous or serosanguineous fluid Subcutaneous hemorrhages may occur When the hyperemia fades the skin of the feet desquamates The anesthesia disappears quickly in the proximal areas but slowly in the distal areas where nerve damage is more severe

Treatment should be directed toward avoidance of further injury reduction of hyperemia and edema and maintenance of strict asepsis The limbs should be kept cool and elevated until the hyperemia subsides Moderate cooling reduces hyperemia promotes resorption of edema fluid and blebs prevents hemorrhage into the tissues and minimizes pain If pain is not diminished or abol ished by cooling opiates are used and even nerve crush may be considered Sympathectomy is inadvisable in the hyperemic stage but may be indicated after recovery Protein and vitamin deficiencies probably contribute to the edema and pain

Chilblain and pernio (erythrocyanosis) deserve men tion because of their relation to immersion foot Al though also due to exposure to cold they are seen most commonly in patients with a history of cool limbs in summer and winter This suggests that they are liable to occur on the basis of a pre existing circulatory dis turbance in the limbs

Frost bite in contradistinction to immersion foot chil blain and pernio is due to freezing of the tissues with mechanical disruption of cell structure It often occurs in association with one of the other syndromes Thawing should be slow to reduce secondary tissue damage that occurs during the excessive local reaction when thawing

dicated that diseased limbs have constantly as great a blood flow as is possible in response to the stimulus of blood flow deprivation, hence the futility of attempting to increase arterial blood flow in such limbs by reactive hyperemia especially with such an ineffective method as venous occlusion

Recent studies indicate that positive external pressure greatly decreases blood flow whereas negative external pressure does not significantly increase it in the limbs Therefore it seems doubtful that alternate suction pressure technics are of benefit in improving blood flow

If diseased arteries are capable of further dilatation warming the body should be helpful temporarily in improving nourishment of the tissues However local heat unless properly controlled may do more harm than good.

Surgical sympathectomy is most clearly indicated when it can be shown that reflex sympathetic vasoconstriction plays an important role in causing ischemia. This may be demonstrated by producing reflex vasodilatation or by functional sympathetic block If there is definite improvement in blood flow after such a procedure it is reasonable to expect a similar result after surgical sympathectomy Following preganglionic sympathectomy the skin of extremities with arterial disease often improves in color and temperature However, it has been questioned whether this necessarily indicates improvement in general nutrition in the limb

Submarine warfare has focused attention on immersion foot which does not differ in etiology and pathology from trench foot observed in World War I In both conditions the lesion is caused by temperatures sufficient to chill but not to freeze the tissues Shipwrecked sailors exposed to cold for prolonged periods develop swollen discolored anesthetic and even pulseless extremities the distal portions usually being affected most severely Dependency and immobility of the limbs add to the swelling and possibly to the severity of the vascular lesions In the [illegible] the

seems probable that thrombosis has occurred Moreover rest immobility local heat and elevation of the limbs may be inadequate to prevent embolization Venous ligation is recommended Unilateral ligation may not be sufficient since the predisposing factors to phlebothrombosis operate generally and quite often thrombosis is present in both legs Ligation should be performed high enough to preclude the possibility of embolization from proximal extension of the clot

Thrombophlebitis is less frequently a source of pulmonary embolism because the associated inflammatory reaction organizes the clot and prevents its breaking off However if the thrombus extends proximally the fresh clot may not be sufficiently adherent and emboli may be broken off by the current of blood Therefore the same therapeutic measures as in phlebothrombosis should be considered In addition if the extremity is cold painful sweaty pale or cyanotic procaine block of the sympathetic ganglions is recommended for relief of arterial spasm Heparin is the anticoagulant of choice given intravenously its action is immediate and may be controlled by varying or stopping its administration by giving protamine or by transfusions of plasma or blood Dicoumarin has several disadvantages Its action is delayed and unpredictable and since it has no effective antidote its control may be difficult

Vascular Disorders of the Extremities John Homans[8] (Peter Bent Brigham Hosp) discusses tests for peripheral arterial deficiency In all vascular deficiencies an estimate of reduction of the arterial supply and amount of the collateral circulation should be made A rough estimate of arterial blood flow is secured by observing color of the toes when the legs are elevated to a 30 degree angle for one to two minutes (rapid paling is unfavorable persistence of pinkness is favorable) and when they are depressed (delay in appearance of pinkness followed by rubor is unfavorable rapid appearance and persistence of pinkness is favorable)

(8) N w E gl d J M d 6 9179 J n 4 194

is too rapid Thus the time honored remedy of applying cold to a frozen area has a rational basis Rubbing or friction further traumatizes already damaged tissues

Varicose veins are best treated by surgical ligation excision or injection Unless the possible variations in the superficial venous drainage are taken into account, varicosities are liable to recur Furthermore following therapeutic injection of the superficial veins chemical thrombosis may extend into the communicating and deep veins and cause post treatment edema and pain This complication has been treated with heparin

Varicose veins when extensive may be responsible for cardiovascular symptoms such as fatigue exertional dyspnea dizziness precordial distress and syncope in the orthostatic position Some patients have been greatly relieved by proper treatment of their varicose veins

Phlebothrombosis is accompanied by little or no local inflammatory reaction to signal its presence or to fix the thrombus in place Its first sign may be occurrence of embolism in the lungs Conditions predisposing to venous thrombosis such as myocardial failure malignancy obesity, debility severe infections varicosities trauma and surgery probably operate in a variety of ways One of these is to slow the circulation in the limbs Other factors recently suggested as possibly important in predisposing to phlebothrombosis include occurrence of hyperprothrombinemia after surgical operations and development of cold agglutinins after certain infections

Deep breathing bicycle exercises and flexion and extension of the extremities are useful in speeding the circulation and lessening the danger of venous thrombosis Measurement of the circumference of the limbs and the use of Homans maneuver—dorsiflexion of the foot to elicit pain in the calf or popliteal space or both—should be done daily to detect the presence of phlebothrombosis Determinations of venous pressure especially after exercise of the limb may indicate the presence of local venous obstruction

Active or passive motion is contrain[illegible]

cases of generalized functional vasoconstriction such as is present in cyanotic sweaty extremities the tests disclose this state and predict relief by sympathectomy These tests may fail in two respects They do not foretell the result of sympathectomy in improving over a long period the nutrition of the feet in the serious arterial deficiencies of both thrombo angiitis obliterans and arteriosclerosis and they may not relax the most serious gross arteriospasms such as those rarely associated with thrombophlebitis and trauma

The Effect of Smoking Cigarets on the Peripheral Blood Flow was studied by Willis F Evans and Harold J Stewart[9] (Cornell Univ) by a method with which the average amount of blood allotted to the periphery can be measured in cubic centimeters per square meter per minute Peripheral blood flow was measured in 10 normal male subjects Effects on the electrocardiogram basal metabolic rate blood pressure and pulse rate were also recorded Studies were made before during and after the smoking of regular cigarets commercially denicotinized cigarets and cigarets made from cornsilk Four observations relating to fully denicotinized cigarets were made on three of the subjects Measurements were made also when two of the subjects smoked cigarets through a water pipe

A decrease in peripheral blood flow occurred in every instance regardless of the type of cigaret smoked (Fig 68) After cessation of smoking the peripheral blood flow continued to decrease in some cases and began to return toward control levels in others In all a return toward normal had begun by the end of 30 minutes after smoking

An increase in blood pressure and pulse rate of essentially the same magnitude and duration resulted from smoking every type of cigaret

The average skin temperature decreased in all but five experiments The hand temperature fell in every instance but two The foot temperature always de

(9) Am Heart J 26 78 91 J ly 1943

In connection with the degree of arterial deficiency, the level at which the arteries are seriously constricted or occluded can be discovered by oscillometry and the histamine test After the state of the peripheral pulses in the feet and legs has been ascertained the vigor of the pulse wave at various levels should be observed with the anaeroid sphygmomanometer With the cuff firmly applied somewhere in the calf and inflated to a pressure between diastole and systole, normal excursion of the needle with each pulse beat will be 1 5 3 mm An excursion of 0 5 mm or only a trace in one leg as compared with an excursion of 1 to 2 mm in the other indicates that a large vessel is occluded at the level tested or higher Such an observation is frequently made in thrombo angiitis obliterans When pulsations in both feet are absent, oscillometry may call attention to a thrombosis decidedly higher in one leg than in the other Presence of serious occlusion at some particular level may also be noted by the histamine test Before this test is made any overlying functional vasoconstriction should be overcome as by gently warming the skin with the hands The test is performed by placing a drop of 1 1 000 solution of histamine acid phosphate on the dry clean skin needling the skin several times through the drop and feeling for a wheal If a wheal fails to appear in three to five minutes the tissues are so ischemic that an incision at or below the level tested as for amputation is unlikely to heal Presence or absence of a satisfactory wheal low in the leg has useful prognostic significance when the problem is not one of immediate amputation The worth of various vasodilatation tests i e, of the patient's capacity for vasodilatation in response to various stimuli and to sympathetic paralysis (heating the other extremities heating the body administering foreign protein sympathetic procaine block spinal anesthesia etc) has been discussed by others In the presence of organic arterial deficiency, these tests demonstrate the capacity of the remaining arteries for dilatation and in general the availability of the collat--

Since these changes occur after smoking cigarets which do not contain nicotine as well as those which do they are not to be attributed to nicotine It is suggested that sympathetic stimulation brought about by the irritating effect of smoke on the respiratory tract may be responsible Smoking cigarets of any type should be avoided in the presence of peripheral vascular disease

Role of Insulin Free Histamine Free Pancreatic Tissue Extract in the Treatment of Peripheral Vascular Disease L W Gorham and D R Climenko[1] (Albany Med College) present objective proof of the physiologic activity of this extract When used on animals and on normal human controls it caused peripheral vasodilatation in the limbs as measured by an increase in volume and a rise in temperature It had a most beneficial symptomatic effect on nearly all of a group of patients with peripheral vascular disease in which vasospasm was a prominent feature Relief was obtained for one to six months with administration at intervals of two to seven days

The series of patients treated consisted of 21 with established or suspected arterial disease The group included cases of established Raynaud s disease Buerger s disease arteriosclerosis with hypertension thrombophlebitis and scleroderma In 15 of these cases the response to cold was of the spastic type These patients reacted especially well to the extract All of them showed significant increases in limb volume and rises in skin temperature Symptomatic relief was complete in eight cases and partial in four The three patients in this group with spastic response to cold who failed to benefit symptomatically after administration of the extract had Buerger s disease or thrombophlebitis Six patients in the group of 21 gave a normal response to cold stimulation i e they showed no evidence of vasospasm None of these patients received any benefit from injections of the pancreatic extract One of them a patient with Raynaud s disease was asymptomatic as a result of pre

(1) Am H t J 5 486 504 Ap 1 1943

creased The decrease in foot temperature was greater than that in hand temperature on all but two occasions

Rapid rises in rectal temperature occurred in all experiments but one These rises were considered an important index to peripheral blood flow

As the result of smoking small increases in basal meta

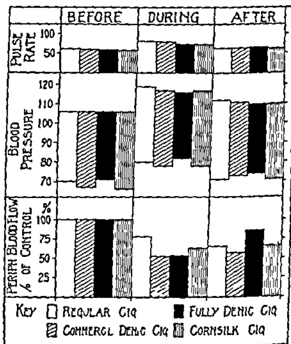


Fig 68 —Chang s in a e ag p phe l bl d fl w a pe e nt of control levels average blood p e d age pul e i a f all subj ts be o during and fter smok g egula c mm lly dent ot d nd fall denicotinized g tt nd th s m d f m i k

bolic rate were observed about twice as often as small decreases The change had no relationship to the kind of cigaret and was of about the same amount and duration as the changes which occur when normal subjects lie in bed for the same length of time without smoking

Electrocardiographic changes were slight and probably of no significance

in addition hot wet packs should be continuously applied locally to hasten absorption An excellent measure is the use of infra red radiation or diathermy every hour for 15 to 30 minutes Elastic support should be used as soon as the pain is gone and the patient may resume his usual routine four to six days after onset

In treatment of deep thrombophlebitis bed rest is instituted and the extremity is elevated on two or three pillows Reflex vasodilatation is induced by placing a large heated cradle over the patient s abdomen Salt is restricted and fluids are limited to 1 000 cc daily to combat edema In addition to these conservative measures any one or a combination of the following procedures may be used Paravertebral block of the sympathetics should be performed immediately if warranted by signs and symptoms Diathermy should be applied over the lower part of the back and the hip of the affected extremity in conjunction with sympathetic block these treatments should be given hourly to aid sympathetic relaxation Artificial fever therapy may also be used to aid sympathetic relaxation and to increase metabolism Temperature should be elevated to 103 104 F for two hours once or twice daily

Peripheral Circulation in Relation to Trauma with special reference to thrombosis and embolism is discussed by Arthur W Allen[3] (Harvard Univ) Recently it was found that 95 per cent of fatal pulmonary emboli occurred without evidence of previous thrombosis The patients had not complained of any discomfort in their legs and had had no change in pulse temperature or respiration The emboli originated in the deep veins of the leg Further analysis showed that in patients aged 25-45 there were few deaths although many experienced pulmonary infarcts most of these recovered on conservative treatment Among those over 45 however the number of fatal emboli increased to such extent that femoral vein ligation is now performed when there is any indication of phlebothrombosis or thrombophlebitis.

ganglionic sympathectomy The operation had evidently abolished the abnormal response to cold The other five cases consisted of one of advanced Buerger's disease two cases of arteriosclerosis one of foot strain with no peripheral vascular disease and one of thrombophlebitis with ulceration

Physical Therapy Measures in the Treatment of Peripheral Vascular Diseases are outlined by Emil J C Hildenbrand (Washington, D C)

Arterial Disease —Certain general measures should be instituted in all cases These include rest the degree of which is determined by the severity of the condition The extremity should not be elevated beyond the optimal level this is usually below heart level and at this point the veins are filled but not distended In the absence of ulceration sitz baths and whirlpool baths at 98 to 100 F may be used, if infected ulcers are present however these are treated with compresses of boric acid or magnesium sulfate solution for 30 minutes three times daily Local heat should never be used on the extremity with arterial disease for it only hastens gangrene by increasing local metabolism in the presence of an impoverished blood supply In its stead reflex heat may be produced by application to the trunk of various physical measures such as infra red light short waves, diathermy, electric pads or hot water bottles Immersion of both hands and arms into water at 113 F for 30 minutes three times a day will produce a reflex dilatation in the legs, and vice versa All patients should be subjected to Wright's modification of the Buerger Allen exercises three times a day

Venous Disease — In treatment of superficial thrombophlebitis the extremity should be elevated on one pillow It is rested rather than massaged to prevent embolus formation Ice caps may be applied to the affected area for 24 to 48 hours to limit the periphlebitic process x ray therapy may be used for the same purpose A heated cradle should be placed over the extremity only

(2) South M J 36 ⁻ 4 8 M r h 1943

woolen blankets in an effort to prevent chilling postoperatively This objective would be better accomplished by control of room temperature and avoidance of drafts than by wrapping the postoperative patient in many blankets A second consideration lies in control of post operative rise in intra abdominal pressure Significant in prevention of such pressure rise are avoidance of peritoneal trauma and contamination during operation and overloading the stomach with fluids afterward in attempting to adjust fluid balance Judicious use of the rectal tube early and enemas later aid in relieving accumulation of gas in the intestinal tract Heavy dressings such as tight abdominal binders are avoided

The third measure consists of use of postoperative exercises For these Krebs uses a bicycle machine consisting of a base of wood planking from which arises a simple upright on which bicycle pedals are mounted On the first postoperative day exercises are given for two five minute periods These are increased on subsequent days to 10 minutes twice daily and continued until the patient is out of bed Of 209 patients who had bicycle exercises none developed thrombophlebitis after a sufficient course of treatment One had the exercises for six days and developed phlebitis the tenth day Of 308 patients in the same period operated on without the advantage of bicycle exercises five (1 6 per cent) developed thrombophlebitis

Vasomotor and Other Reactions to Injuries and Venous Thrombosis Changing concepts reviewed by John Homans[6] (Peter Bent Brigham Hosp) indicate that both large and small vessel vasospasms may result from thrombophlebitis and numerous other injuries All blood vessels exhibit vasomotor tonus and present some elasticity All relax when vasoconstrictor impulses are removed although there is uncertainty as to the existence of true vasodilator nerves All except the very largest arteries are capable of forcible contraction when

(6) Am J M S 0 313 3 S M h 1943

Bilateral femoral ligation is essential for cases have been observed in which ligation of the obviously thrombophlebitic vein has been followed by fatal embolism arising from the presumably normal side

It is not uncommon to detect early signs of phlebothrombosis or thrombophlebitis before the patient is aware of any disturbance or before the chart indicates impending complications This may be done by routine bidaily observations of the uncovered extremities Significant points to be observed are whether the superficial veins are filled or empty whether there is any swelling by actual measurements whether there is any tenderness in the calf and most important whether there is a positive Homans sign

When multiple emboli have occurred the patient may well develop considerable difficulty in his chest, which continues even after vein ligation In cases in which apparently *normal veins* have been ligated and sublethal infarcts have subsequently occurred it may be assumed that such infarcts have come from the vicinity of the wound and would not have been fatal under any circumstances Such patients are sometimes helped by heparin

However when thrombophlebitis of the deep veins of the leg does exist removal of the clot and ligation of the vein not only prevent fatal embolism but also cause more rapid resolution of pain and swelling and shorten convalescence

Routine Use of Bicycle Exercises for Prophylaxis of Postoperative Thrombophlebitis is discussed by Joseph M Krebs[4] (St Louis Univ) Several approaches should be used in prevention of thrombosis and embolism The first is maintenance of normal fluid levels achieved by subcutaneous or intravenous administration of fluids Also relevant is control of vomiting diarrhea and hemorrhage An important source of fluid loss frequently overlooked is the sweating induced by use of heavy

(4) Am J Obst & Gyn 44 "3 80 July 194"

woolen blankets in an effort to prevent chilling postoperatively This objective would be better accomplished by control of room temperature and avoidance of drafts than by wrapping the postoperative patient in many blankets A second consideration lies in control of postoperative rise in intra abdominal pressure Significant in prevention of such pressure rise are avoidance of peritoneal trauma and contamination during operation and overloading the stomach with fluids afterward in attempting to adjust fluid balance Judicious use of the rectal tube early and enemas later aid in relieving accumulation of gas in the intestinal tract Heavy dressings such as tight abdominal binders are avoided

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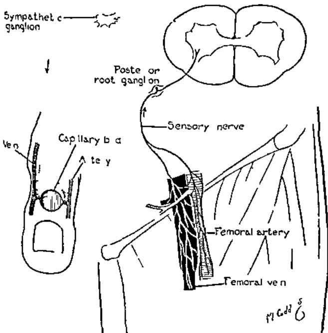
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(6) Am J M S 05 313 328 M h 1943

their sympathetic supply is irritated Sympathetic stimulation, then causes vasoconstriction and sympathetic paralysis vasodilatation These reactions mediated through hypothalamic medullary and spinal cord centers are elicited by cold and by emotion More important however are the effects of vasomotor reflex action caused by severance of or injury to a large vessel. If a great artery to a limb is cut off the arterial branches to the limb dilate with establishment of collateral circulation This reaction is not well protected, however, for if the artery instead of being divided is injured or becomes thrombosed or even is occupied by an embolus the whole arterial tree instead of dilating contracts so that collateral circulation is greatly restricted This reaction can be overcome only by dividing the vessel or the structures immediately about it In this instance there is evidence of impulses running centrally which if unimpeded evoke an outgoing sympathetic stimulus which contracts the branches of the great vascular tree but the interruption of which permits a corresponding vasodilatation The distribution of sympathetic constrictor fibers to the arterial system of any limb indicates that this contraction is not due to local irritation of outgoing sympathetic nerves These constrictor fibers do not run for great distances along the vessels but reach them at successive levels They emerge from the somatic nerves to be distributed to the arteries in a series of branchings and in the end the distribution to the peripheral parts corresponds roughly to that of the sensory nerves to the skin Thus if the sympathetic nerves supplying the femoral artery in the region of the groin are stimulated vasoconstriction in the local area served by these nerves will occur, but the peripheral vessels will remain unconstricted since they are served by sympathetic fibers which have not yet passed out on the arterial tree from the great somatic nerves In other words local stimulation or paralysis of vasomotor fibers causes a relatively restricted direct reaction

Not only are the outgoing vasoconstrictor nerves dis

tributed to a succession of vascular fields but sensory fibers accompanying the arteries and veins of a limb leave these vessels at as yet undetermined intervals to



F g 69 —F m th mb d f m l n rr t t mmu ted th ugh t se ory fil me t v m t c n rv d po t t g nglion to ymp th t c l m t d, whe utfl w g ymp th t co t ct ng imp l s o t ct n f the rt l (nd v ul !) l to the apill ry b d in the rr p nd g t m ty At m t m l l c t ct n f f m l rt y oc u

join the somatic nerves and pass within them to the posterior roots of the spinal cord These sensory nerves are probably associated in a great part of their course with the strictly sympathetic vasoconstrictor fibers but they always end by entering the cord through the pos terior roots Therefore irritation of the sensory filaments attendant on a blood vessel at any point is capable of sending into the central nervous system impulses which may result in a reflex disorder affecting the circulation

in the whole limb (Fig 69) The extent of the reaction appears uncertain and variable, but it tends to be general There may even be a spill over to the opposite limb This makes apparent the difference between the effect of a local vasomotor stimulation and a local sensory stimulation The former is local the latter is more or less general Probably the two often occur simultaneously

Localized arterial spasm may be secondary to acute thrombophlebitis and to injuries such as fractures or wounds by missiles Spasm of the brachial artery may occur in the scalenus syndrome Other primary causes of local spasm include acute arteritis and embolism The peripheral diffuse vasospasm occurring in these conditions may sometimes be followed by a painful causalgia like state Similar painful complexes may sometimes follow seemingly minor trauma The peripheral vasospasm and the causalgia occurring in these conditions may be dramatically relieved by sympathetic paralysis A similar though less rapid and complete effect follows separation of the inflamed vein from perijacent structures In the first case sympathetic block releases the peripheral vasospasm In the second the in going sensory impulses which reflexly excite the sympathetic vasospasm are believed to be modified In either case the favorable effect lasts longer than the temporary character of the procedure warrants

Application of Phlebography to Therapy of Thrombosis and Embolism Claude E Welch Henry H Faxon and Claude F McGahey (Massachusetts Gen l Hosp) describe several methods of phlebography varying as to site and method of injection Details of the roentgenogram and of the medium used were the same in all instances

The first method is that of Bauer After novocain infiltration a 2 cm incision is made at right angles to the Achilles tendon just behind the external malleolus The terminal branch of the short saphenous vein is isolated in the subcutaneous tissue A no 18 ball

(7) Su g y 1 163 183 August 194

pointed needle inserted proximally is tied into the vein The heel of the supine patient is then elevated on a 4 in block The leg is internally rotated 10 15 degrees to secure the widest gap between the tibia and the fibula and two large x ray cassettes are placed in tandem beneath the leg The lower should extend a short distance above the knee since a short blank space will appear between the two cassettes and should not in

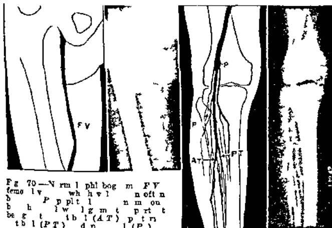


Fig 70—N rm l phl bog m *F V* femo l v wh h v l n oft n b *P* p pl t l n m ou b h l w l g m t p rt t be g t t b l (*A T*) p t n t b l (*P T*) d p l (*P*)

clude this important area To include the entire leg in the field the focal length of the tube should be about 6 ft Twenty five cc diodrast is injected at a steady rate so that exactly 60 seconds are consumed The x ray exposure is taken just at the conclusion of injection using soft tissue technic A normal phlebogram obtained in this manner is shown in Figure 70

If the patient has had deep phlebitis previously, preferential return of the diodrast by way of the long saphenous vein may lead to an erroneous impression concerning patency of the femoral vein To obviate this the foregoing technic is modified by application of a blood pressure cuff to the lower leg The upper edge of the cuff is at the midcalf level and a pressure

of 20 mm Hg is used Accordingly, the long saphenous vein is occluded by the tourniquet and the injected diodrast flows through the deep femoral system

With the third method, injection is made into one of the dorsal veins of the foot or the distal end of the long saphenous vein Return of blood through the long saphenous vein is prevented by use of a tourniquet Prompt filling primarily of the posterior tibial vein by means of numerous perforating vessels in the lower leg is obtained

Arteriosclerosis and Varicose Veins Occupational Activities and Other Factors Michael Lake, Gerald H Pratt and Irving S Wright[8] (Columbia Univ) studied 536 persons divided into age groups, who had been sitting standing walking or climbing stairs for 10 years or more at their work Observations are made on the relation of sex occupation age use of tobacco and alcohol pregnancy and hypertension and the development of arteriosclerosis and varicose veins in the lower extremities

Roentgen examination provided the most important single method of detecting arterial changes However in a few cases arteriosclerosis in the legs was detected by the oscillometer without changes being demonstrable by roentgen examination

While the figures presented are not of sufficient volume to constitute final evidence the statistics suggest that arteriosclerosis of the leg arteries develops earlier in men who climb stairs than in men who do not (see Table) The statistical difference was considered significant for the age group 40-49 but of no consequence in later decades This variation on inquiry did not appear to be due to occupational shift so the reason was not obvious Incidence of arteriosclerosis did not seem to vary significantly in the other three occupational classifications Men showed a higher incidence of arteriosclerosis than did women of the same age groups who had worked at the same types of occupations Had roent

(8) J A M A 119 696 701 J e 27

INCIDENCE OF ARTERIOSCLEROSIS OF THE LEG ARTERIES IN ALL GROUPS IN THE STUDY

Age Groups	Tot	With Art riosclerosis		Disease Revealed by Roentg n Examina ion		Dise se Revealed by Other Evidence
		No	%	Total with Calcifi cat on	No with Calcifi ca ion Only	
Men						
All groups	305	141	46	1 5	115	6
Standers	89	38	43	35	30	3
Walkers	1 9	64	50	6	54	[illegible]
Sitters	40	16	40	16	1[illegible]	
Stair climbers	4[illegible]	3	9		16	1
40 49	137	34	?7	30	?7	4
Standers	40		17	5	5	
Walkers	5?	12	3	11	11	1
Sitters	16	4		4	4	
Stair climbers	9	11		10	7	1
50 59	104	5	55	55	48	?
Standers	3	1		16	15	1
Walkers	49	[illegible]9	59	28		1
Sitters	11	4		4	4	
Stair climbers	1	7		7	7	
60 and over	64	50	77	50	40	
Standers	1	14		14	10	
Walkers	8	3		23	?1	
Sitters	13	8		8	7	
Stair climbers	6	5		5		
Women						
All groups	31	46	0	4	3[illegible]	4
Standers	107	?	21	20	16	2
Walkers	56	10	18	9	6	1
Sitters	66	13	19	1[illegible]	10	1
Stair climbers	[illegible]	1		1		
40 49	1	10	8	10	7	
Standers	48	3	6	3	?	
Walkers	28	4		4	3	
Sitters	46		6	3		
Stair climbers	1					
50 59	81	21	?6	19	16	2
Standers	43	11	27	10	9	1
Walkers	2			?	1	
Sitters	16	8		7	6	1
Stair climbers						
60 and over	[illegible]7	15		13	9	2
Standers	16	8		7	[illegible]	1
Walkers	6	4		3	2	1
Sitters	4	2		2	2	
Stair climbers	1	1		1		

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(8) J A M A 119 696 701 Jan 7 1947

veins Also the women who sat at their work had definitely fewer varicosities than either those who stood or those who walked but the men showed no increase at all on standing or walking as against sitting These observations may be associated with the fact that the supporting tissues of the female are softer and less supportive to the vein walls and also that at times of pelvic congestion there may be a great tendency to venous back pressure Also the high incidence of varicose veins in working women over 40 may be related to the wearing of high heels with resulting compression of the soft vein walls by the leg muscles

There seems to be some evidence in favor of a definite relation between development of arteriosclerosis and varicose veins in men Such a relation in women is not clearly demonstrated by these data

This study will be of interest particularly in connection with the mobilization of men over 40 In addition the necessity of manning and fighting from bases in frigid temperatures such as Alaska and Iceland will increase the importance of the arteriosclerotic problem

Industrial Aspects of Peripheral Vascular Disease are discussed by Lawrence N Atlas[9] The disability arising from injuries to the extremities in persons with peripheral vascular disease is of sufficient moment to merit exclusion of individuals so afflicted from positions in which injury to the extremities may be sustained When the circulation to an extremity is diminished by arteriosclerosis or arteritis slight injury can assume disastrous proportions Chronic ulceration or gangrene threatening the viability of the limb may ensue Such persons should be placed at bed rest Extreme care must be exercised to avoid infection If surgical repair is necessary local anesthesia should not be used and the application of irritating antiseptics should be avoided Suitable measures to increase local circulation should be instituted In the presence of complicating vasospasm paravertebral procaine injec

(9) Oh St te M J 9 38 40 M ch 194

gen evidence been the only diagnostic procedure employed these conclusions would remain the same

While incidence of subnormal oscillometric readings was small in this series of actively employed persons, the oscillometer was responsible for detecting a larger percentage of arterial disease in women than in men

Of the men who had calcification, 41 showed 3 and 4 plus roentgen changes Of the women, five showed 3 plus changes none showed 4 plus changes The old explanation for such observations namely, that women have a more sheltered and less active existence was clearly eliminated The explanation is not completely clear but the results of an experimental study of cholesterol fed rabbits is of interest Ludden, Bruger and Wright found that administration of testosterone propionate and estradiol dipropionate exerted no noteworthy influence on the development of arteriosclerosis in male rabbits fed cholesterol In female rabbits however development of hypercholesteremia was definitely inhibited and deposition of cholesterol in the aorta was prevented by administration of these steroid hormones In later studies Bruger showed that castration prevented this protection in the female It appears therefore that at least in man and rabbits there is a definite difference between the sexes in the reaction of the arterial walls to atheromatous changes

Neither tobacco nor alcohol had any effect on development of arteriosclerosis

Incidence of arteriosclerosis was considerably greater among persons with hypertension than among persons with normal blood pressure

Many subjects with definite arteriosclerosis some with considerable calcification had no complaints of pain or fatigue in the lower extremities

A decided difference between the sexes was noted in incidence of varicose veins (40 7 per cent in men 73.2 per cent in women) While pregnancy accounted for some of this variation even among the women who had never been pregnant 67 per cent . .

line strychnine and prostigmine, none of which altered intramuscular pressure Blood transfusions and saline or glucose intravenously were also without effect All these substances had no effect on the intramuscular pressure when low

Coramine however promptly and spectacularly increased intramuscular pressure from a low level to the normal When given intravenously in 5 10 cc doses it rarely failed to restore intramuscular pressure and with it a low venous pressure to normal Doses as high as 30 cc in 30 minutes given intravenously have been used in normal individuals and 20 cc has been given to a patient in shock to produce the therapeutic effect The drug has been used in postoperative depression postoperative shock acute massive hemorrhage with shock and shock accompanying coronary occlusion Its use following massive hemorrhage and shock is particularly interesting as the venous circulation was restored without the pressor effect seen in normal persons The pressor effect of coramine was also absent in other shock states

The peripheral circulatory support obtained by use of coramine should permit survival until such time as serum and other therapeutic procedures can be instituted

Varicose Veins and the Soldier Willson Pepper (R A M C) combines injection treatment with ligation of one or more veins and in this manner has been able to discharge most military patients with seemingly good results in a comparatively short time Sodium morrhuate 5 per cent is used as sclerosing agent Successful results following ligation depend on observance of certain factors in performing the ligation Thus in some cases saphenous ligation is performed too low so that subsidiary veins joining the main vessel between the ligature and the entry to the femoral vein have not been blocked. In others the reflux occurs lower down the thigh or from the popliteal vein so that the usual

(2) J Roy Army M C 79 30 33 July 1942

tions of the sympathetic ganglions or sympathectomy may be considered necessary to secure healing

In some instances injury appears to initiate a pathologic process clinically indistinguishable from Buerger s disease Such traumatic arteritis may spread with great rapidity uninfluenced by any treatment and the extremity is eventually lost However, there exists another *type of traumatic arteritis which is more* amenable to treatment In cases of this type a contusing injury to the terminal phalanx of a finger or toe is shortly followed by excruciating local pain The injured digit becomes swollen stiff discolored and frequently cold There is considerable reflex vasospasm and the entire hand or foot may become cold cyanotic and sweaty As dystrophy progresses the injured phalanx becomes gangrenous and ulcerated These cases respond well to sympathectomy pain is relieved *the gangrenous tissue demarcates and separates,* and ulceration heals

It is also possible for local injury to aggravate the severity of a pre existing arteriosclerosis or arteritis This is caused by thrombosis and reflex vasoconstriction and results in destruction of the favorable balance which existed between the collateral and the diseased circulation prior to injury Unless other collaterals develop the diminution in peripheral circulation may be permanent

Intramuscular Pressure According to Lewis Gunther[1] (M C U S N R) intramuscular pressure is a factor of greatest importance in maintenance of peripheral circulation It is a determinant of venous pressure and the volume of venous flow and cardiac filling Without it peripheral circulatory failure and collapse ensues Many agents were tested for their action on intramuscular pressure Among these were morphine sulfate atropine sulfate ephedrine paredrine barbitu rates acetylsalicylic acid carbon dioxide inhalations oxygen inhalations caffeine sodiobenzoate aminophyl

(1) U S N M B 41 [illegible]

ily by taking careful circumferential measurements at set points in the thigh calf and ankle then applying Ace type bandages and tourniquets with the veins empty permitting the patient to walk for 10 minutes and then remeasuring Increase in size of the limb or pain is an indication of deep vein closure In testing for adequacy of the saphenous femoral valve, the patient s leg is elevated and the veins emptied A tourniquet is applied high in the groin and the patient allowed to stand When the tourniquet is removed a rapid filling of the veins from above indicates valve failure Incom petency of the communicating branches is tested for by applying an Ace bandage from the toes to the groin and a tourniquet on the thigh above this area As the bandage is removed a sudden protrusion of a collection of veins shows the point of incompetence

TECHNIC — Only local anesthesia should be used The saphenous vein at the femoral junction will be found 1 in lateral and 1 in below the spine of the pubis Elevation of the saphenous vein with a tape assists in demonstration of each of the branches entering the bulb After resection of the branches the saphenous vein should be divided 3 or 4 in below the bulb dissected up to the femoral junction and ligated flush with the femoral vein by a transfixion suture The distal end is then opened and the saphenous vein sclerosed by the retrograde insertion of a solution through a ureteral type catheter If there are no contraindications (arterial dis ease open ulcer) about 20 to 40 cc of 3 5 per cent sodium moroleate may be introduced The distal end of the saphenous vein is then resected transfixed and ligated While the saphenous vein and its branches are being exposed in the groin an assistant dissects the secondary points together with a section of the saphenous and the communicating branch. These are resected at the time the solution is introduced The wounds are closed without drainage and are sealed pressure pads are placed along the course of the saphenous vein and an Ace type bandage is applied from the toes to the groin The patient walks around the room at once and thereafter for 15 minutes out of every hour At the end of an hour the upporting bandages are removed and the legs inspected for collections of excess sclerosing solution as shown by dis colorations Extra pressure pad are applied at these points and the bandage is reapplied

ligation of the saphenous vein at its upper end is too high to be effective These errors may be obviated by test before operation to ascertain the point of reflux. This is done by elevating the leg with the patient supine emptying the veins by central massage applying the tourniquet and then having the patient stand. If the tourniquet is above the reflux site, the varicose veins below will quickly fill if below, they will remain empty or at the most fill gradually Another precaution which will facilitate location of the vein after incision is to mark the skin above the vein while the patient is standing

Patients should be warned that successful operation and thrombosis may be followed by some discomfort Aching stiffness and tenderness sometimes lasting several weeks has been observed to follow extensive thrombosis

Soldiers should be hospitalized for a week following ligation and should not be returned to duty for another week if extensive thrombosis has occurred These patients should not be kept in bed however, even immediately after operation for by elevation of the leg the affected veins will empty more readily and serve to diffuse the sodium morrhuate into the general circulation with consequent risk of pulmonary embolism or general reaction

Results of Surgical Treatment of Varicose Veins Gerald H Pratt[3] (Columbia Univ) states that when the major valves connecting the superficial and deep vein systems are incompetent surgical treatment is the only type that can be helpful This is true in 60 to 80 per cent of patients seeking treatment for varicose veins

Certain tests are important in selection of patients for operation The arterial supply should be estimated although arterial disease is no longer a contraindication to operation on varicose veins Determination of deep vein patency is essential A test can be done read

(3) J A M A 1 797 600 July 17 194

ing is applied The lesion is re examined within one to three days, and if the clot has been broken up or liquefied the pro cedure is repeated For complete healing 1 20 applications of blood may be necessary The larger the lesion, the greater the number of applications Patients should rest as much as pos sible during treatment

A modified method was used on some patients with large lesions Five cc the patient s blood is placed in an ordinary



Fig 71 (l ft) —I hem ul p t t w th d bet s m llitus, bef e t tm t D t f ul 13 m th
Fig 72 (right) —S m se ght w k l t mpl t ly h l d fte 17 appl c t s of p t nt own bl d.

sterile nose and throat atomizer The surface of the ulcer is then sprayed and the blood allowed to clot in the manner described

Concentrated plasma has also been used This is prepared by diluting dried plasma with only one quarter the amount of distilled water which would ordinarily be used to restore it to normal concentration This concentrated plasma therefore contained eight times the amount of clotting elements and other substances minus red and white cells present in an equal volume of whole blood It is applied in the same manner as whole blood Concentrated pl sma instead of the patient s blood can be used in thos with a positive blood Wassermann reaction

The author and his associates have re examined and obtained follow up results on 357 patients operated on during the last six years Results were excellent (symptom free no recurrence and less than 4 subsequent injections) or good (symptom free, no recurrence and less than 11 subsequent injections in 89 5 per cent of the males and 93 2 per cent of the females treated Some local recurrences were seen in 6 per cent of the males and 4 9 per cent of the females There were 4.5 per cent failures in the males and 1 9 per cent in the females

Pratt emphasizes that varicose veins as a result of phlebitis are a different type of vein Treatment must be varied and the results cannot be as satisfactory as in the simple varicosities Contraindications to the operation described are (1) active and continuing phlebitis (2) closure of deep veins and (3) presence of an acute infection such as a cellulitis in the leg

Treatment of Leg Ulcers with Blood and Concentrated Plasma Meyer Naide[4] (Univ of Pennsylvania) describes a simple method for treatment of ischemic and varicose leg ulcers with the patient s own blood and with concentrated plasma Nine of 15 ulcers refractory to other treatment were healed 2 were improved and 4 failed to heal This treatment results in rapid relief of pain and subsidence of the local inflammatory reaction

METHOD —The ulcer is cleansed gently with hydrogen peroxide and mopped with sterile gauze One to 5 cc blood is drawn into a sterile syringe from the patient s antecubital vein The blood is applied to the ulcer surface simply by placing a number of drops on it sufficient to cover the lesion The drops may be smeared or spread over the ulcer surface so that a blood film of any desired thickness may be obtained One cc blood will cover an area of approximately 30 sq cm so that only a small quantity of blood is required The blood is permitted to clot the leg being held in such a position that the blood does not run off the ulcer Clotting time in air is 30 120 minutes this may be shortened to 15 60 minutes by use of a fan After a solid clot has formed a sterile dry dres

(4) Am J M Sc 05 4 9 493 April 1943

ing is applied The lesion is re examined within one to three days and if the clot has been broken up or liquefied the procedure is repeated For complete healing, 1 20 applications of blood may be necessary The larger the lesion the greater the number of applications Patients should rest as much as possible during treatment

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Fig 71 (l ft) —I h m ul p t nt w th d b t m ll tu b f t tm t D t on f ul 13 m th

F g 7 (right) —S m ht w k l t mpl t ly h led fte 17 ppl t f p t nt wn bl d.

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DISEASES *of the* DIGESTIVE SYSTEM *and* METABOLISM

GEORGE B EUSTERMAN M D

PART V

DISEASES OF THE DIGESTIVE SYSTEM AND METABOLISM

INTRODUCTION

Despite a war of global dimensions and the unprecedented demands on the medical profession the quality and volume of scientific contributions during the current year are surprisingly up to the usual standard This is indicative of the vigor resourcefulness and sustained scientific interest of the medical fraternity individually and collectively Because of their immediate and future significance to medical practice we showed some favoritism in the selection of articles dealing with military medicine especially with the diagnosis and treatment of tropical diseases We can look forward to an increasingly large number of contributions of the highest order in the months to come and especially after cessation of hostilities by American authorities at the far flung fighting fronts

—GEORGE B EUSTERMAN

DISEASES OF THE STOMACH AND DUODENUM

Acidity of Ulcer Bearing Area of Duodenum in Normal Persons To determine the role of the acid factor of the duodenal bulb in causing and maintaining chronic peptic ulcer J Edward Berk Martin E Rehfuss and J Earl Thomas[1] studied 23 normal subjects aged 22 51 selected mainly from the outpatient gastrointestinal clinic of Jefferson Medical College Hospital

A *subject was considered normal if there was no* evidence of fever or of any acute chronic infectious metabolic or cachectic disease liable to affect gastric secretion and if x rays of the stomach and duodenum were normal

Subjects were examined before breakfast and after a 12 hour fast Material was aspirated at 10 minute intervals from the pars pylorica and duodenal bulb by a specially constructed double lumen tube Specimens were taken for one half hour in the fasting state and

(1) Am J D g st D 9 2 6 80 S ptember 194

for two hours following ingestion of an Ewald meal consisting of two pieces of dry toast or stale bread and 250 cc tap water A Leeds Northrup pH indicator was used to determine the pH of each specimen and free and total acidity were then estimated In addition excess *neutralizing ability* was determined for each specimen

The authors conclude that in normal persons the important ulcer bearing first part of the duodenum is an acid area whose average pH in the fasting state is about 5 6 and after an Ewald meal about 5 The duodenal bulb has a capacity to neutralize, buffer and dilute gastric chyme which generally exceeds the physiologic needs Free acid in the duodenal bulb, although usually absent cannot be construed as abnormal Following an Ewald meal neutralizing ability of the contents of the first part of the duodenum is ineffective usually however only for a brief period

Increases in gastric acidity do not appear to be accompanied by corresponding increases of duodenal *acidity* Gastric *acidity per se is only one* factor concerned in regulating the reaction of the duodenal contents

Experimentation has shown that the neutralizing power of the duodenal bulb contents in normal man is not as great as in normal dogs

Effect of Gastric Hypersecretion on Reaction and Neutralizing Ability of Contents of First Part of the Duodenum in Normal Dogs J Edward Berk J Earl Thomas and M E Rehfuss[2] (Philadelphia) attempted to produce temporary gastric hypersecretion in normal dogs by the simultaneous action of histamine and Liebig s extract for the purpose of observing its effects on the reaction and neutralizing ability of the *duodenal* bulb

During the early postprandial period there was a more or less precipitous increase in acidity in the duodenal bulb and more than the usual volume of duodenal

( ) Am J Digest D 9 297 301 Sept m

contents indicating gastric hypersecretion and rapid emptying of the stomach Gastric hypersecretion and rapid stomach emptying frequently interfere with adequate neutralization in the duodenal bulb Impairment is usually slight and is rapidly corrected but in some instances neutralization may be inadequate for considerable periods No good correlation exists between the degree of gastric acidity and the reaction and neutralizing ability of the contents of the first part of the duodenum

None of the customary measures of acidity in the stomach can be relied on to indicate the behavior of the corresponding effective acidity (pH) in the first part of the duodenum

[The significance of research of this nature lies in the fact that of all the benign lesions of the upper d gestive tract to which human flesh is heir duodenal ulcer is by far the most frequent Th acid factor in the genesis and treatment of this lesion cannot be ignored It is fervently to be hoped that research of this nature will contribute to further progress both from the med cal and from the surgical therapeutic standpoint —Ed]

Studies on Experimental and Clinical Hypochloremia in Man conducted by Joseph B Kirsner Walter Lincoln Palmer and Kathryn Knowlton[3] (Univ of Chicago), demonstrate that a severe hypochloremia is not necessarily accompanied by azotemia The important factors which determine the extent of urea nitrogen elevation during hypochloremia apparently are the speed with which chloride loss is induced and the degree and rapidity of dehydration associated with chloropenia An abrupt depletion of chloride is associated with an equally abrupt and marked loss of sodium and therefore of body water Loss of fluid decreases the circulating blood volume which by reducing the venous return to the heart presumably lowers the cardiac output This course of events may actually lead to peripheral circulatory failure The blood flow through the kidney and the effective glomerular filtration pressure are consequently lowered The severe nitrogen retention and decreased renal function noted under

these conditions by other workers evidently represent a decreased renal circulation rather than intrinsic renal disease Absence of azotemia during hypochloremia in the present experiments may be attributed to two factors (1) gradual deprivation of chloride, allowing the patients to make fairly satisfactory adjustments to the severe electrolyte changes, and (2) daily administration of large quantities of water which tended to 'wash out' the urea nitrogen and apparently maintained an adequate blood flow through the kidney It was also observed that gastric secretion in man is not altered significantly by severe hypochloremia

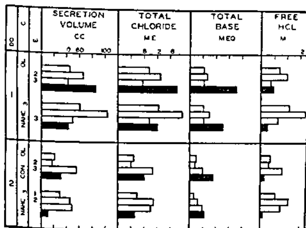
Effect of Sodium Bicarbonate on Gastric Secretion Using a new technic employing the recently described Cope pouch dog W Lloyd Adams C Stuart Welch and Byron B Clark[4] (Albany Med College) studied the changes produced in gastric secretion by a 1 5 per cent and a 2 per cent solution of sodium bicarbonate administered three times daily in doses of 50 cc by stomach tube and a 4 per cent solution placed directly in the pouch The objective of the technic used was to approach normal physiologic conditions as closely as possible while allowing continuous observation of secretory activity rather than observation for a few hours following a test meal

Sodium bicarbonate produced an increase in gastric secretory activity during the hours immediately following a test meal with a partial compensatory decrease during later hours In all cases the volumes during the first nine hours showed increases ranging from 2 5 to 38 per cent At the same time five dogs showed increases in total chloride while one showed a slight decrease Decreases in volume during the night ranged from 8 8 to 61 per cent and in chloride from 20 to 37 per cent The daytime increases were characterized by appearance of relatively larger amounts during the earlier periods of collection (Fig 73) Further changes effected by sodium bicarbonate are seen in the signifi

(4) Am J Phy i l 139 356 363 J ly 1943

cant net decrease in total base and the marked net increase in free acid Thus sodium bicarbonate acts to elicit a higher percentage of total chloride as free acid to meet the need of more free acid to neutralize the alkali

It is evident from these studies that neither fractional gastric analyses nor pouch studies for a few



F g 73 —A ag tory p e f Cope p u h d ng tw w ek of feed g 50 c f 2 p t N HCO th t m d ily mp ed w th v g p d g tw w ks f t 1 C mp by ll ti period 1 to 4 wh h 8 11 11 2 5 n d yt m (p b) d f m 5 P M to 8 A M (bl k b)

hours after a test meal provide adequate data to reveal the effect of antacids on gastric secretion Previous reports have shown that an increase in acid concentration may occur The present data suggest that the rebound or secondary acid concentration observed by fractional analysis after ingestion of sodium bicarbonate results primarily from the shift in gastric secretory activity This brings a greater part of the secretion elicited by a test meal into the stomach at an earlier period and is accompanied by an increase in the amount of acid secreted

Studies on the Effect of Massive Quantities of Sodium Bicarbonate on the Acid Base Equilibrium and on Renal Function Although considerable emphasis has been placed on the development of alkalosis during alkali treatment of peptic ulcer this complication does not occur in most patients so treated Recent studies have indicated that therapy may be continued for many years without significant alteration either in the acid base balance or in renal function Jo eph B Kirs ner and Walter Lincoln Palmer[5] (Univ of Chicago) report a case which well illustrates this remarkable tol erance to alkalis In this patient the ingestion of 32,000 Gm sodium bicarbonate in 20 months produced only minimal changes in the acid base equilibrium and no demonstrable decrease in urea clearance

Man, 23, had had ulcer distress for five years, during which time he was hospitalized twice because of massive hemorrhage Alkalosis was said to have been present once as a result of excessive ingestion of alkali following appearance of tarry stools Physical examination was negative except for localized epigastric tenderness Roentgen studies disclosed a stenosing duodenal ulcer with a crater measuring 15 mm in diameter The patient was observed in the hospital for 11 months and subsequently in the clinic for 16 months a total of 27 months

The basic diet in the hospital consisted of 90 cc equal parts of milk and cream taken at hourly intervals from 7 00 a m to 7 00 p m Feedings consisting of soft bland foods were added gradually so that after four weeks the patient received a modified three meal ulcer diet with milk and cream hourly After discharge the quantity of milk and cream was decreased and the three meal program enlarged The protein intake although somewhat reduced during the initial four to six weeks was consistently above basal requirements averaging 55 Gm daily for the first month (Sept 3 30, 1938), 77 Gm during the second month (October 1 31) and 102 Gm daily between November 1 and 30 The protein intake during December averaged 88 Gm a day and was maintained at approximately this level for the remainder of the study

Fluid intake and output were measured daily between November 1938 and August 1939 and are recorded as averages per day during each month in the table The large quantities of alkali administered precluded occasional efforts to reduce the 24 hour fluid intake below 3 000 ...

(5) Ann Int Med 18 100 104 Ja u ry ...

tents were aspirated nightly for a six month period (November 1938 to April, 1939) The quantities removed varied widely, ranging from 30 to 900 cc the average daily amounts are noted in the table The volume of aspirate per day gradually decreased from an average of 388 cc in November 1938 to 143 cc in April 1939

Alkali therapy was continued for 20 months intake per month is shown in Figure 74 Between Sept 6 and 30 1938 the patient received 135 Gm sodium bicarbonate 219 Gm calcium carbonate and 352 cc aluminum hydroxide During

AVERAGE DAILY FLUID INTAKE AND URINARY OUTPUT AND GASTRIC ASPIRATION

	Av Daily Fluid Intake Cc	Av Daily Urinary Output Cc	Gastric Aspiration: Av Daily Amount Cc	Gastric Aspiration: No Days Aspirated
Nov 1938	3 478	2 458	388	10
Dec. 1938	3 [illegible]5	2 [illegible]39	347	[illegible]7
Jan 1939	3 718	2 9[illegible]3	28	2
Feb 1939	5 011	3 936	2[illegible]8	8
Mar., 1939	4 951	3 378	188	9
Apr 19 9	4 88	3 377	143	[illegible]5
May 1939	4 3 6	6 0		
June 1939	4 4	780		
July 19 9	3 446	1 79[illegible]		

October 48 cc aluminum hydroxide 302 Gm calcium carbonate and 830 Gm sodium bicarbonate were given Massive quantities of sodium bicarbonate were administered between Nov 1 1938 and Apr 22 1940 The daily intake averaged 90 Gm for the eight month period between Nov 1 1938 and Aug 1 1939 The quantity of alkali was then gradually reduced to 60 Gm daily between Aug 1 and Dec 1 1939 and for the five month period between Dec 1 1939 and Apr 22 1940 averaging approximately 30 Gm a day The total amount of alkali administered during the 20 months consisted of 400 cc aluminum hydroxide 881 Gm calcium carbonate and 31 414 Gm. sodium bicarbonate Alkalis were taken only occasionally during the final seven months (Apr 23 to Nov 13 1940) and the intake was comparatively small

T

content remained within normal limits Three histamine tests disclosed a maximum free acidity of 118, 110 and 150 clinical units Forty five urine specimens were examined the specific gravity varied from 1 015 to 1 034, averaging 1 024, the reaction was constantly alkaline a trace of albumin was detected on four occasions Numerous electrocardiograms revealed no significant changes The clinical course was uneventful The ulcer crater disappeared in five weeks and did not reappear

The acid base balance was determined 78 times (Fig 74) The serum carbon dioxide during hospitalization varied usually from 31 to 35 mM /L (normal 20 30 mM /L) with increases to 37 7 and 39 2 mM /L on two occasions *After discharge*

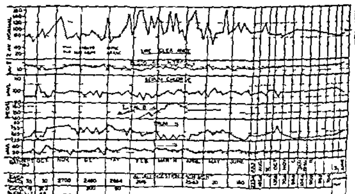


Fig 74 —Serum lectrolyt s and u ea cl a ance duri g cont ued sod um b b nat administration

charge from the hospital the carbon dioxide remained within normal limits The serum pH paralleled the carbon dioxide and fluctuated usually from 7.33 to 7 50 (normal 7.35 7 45) although values between 7.50 and 7.53 were noted frequently The total base was determined on 18 occasions, only *two* of the results (163 4 and 164 9) exceeded the normal range of 150 160 m Eq /L The serum chloride was consistently within the normal limits of 95 to 105 mM /L

Two urine concentration tests before alkali therapy revealed maximum specific gravities of 1 025 and 1 027 Three urea clearance tests during the control period measured 60 75 and 80 per cent of average normal respectively (lower limit of normal considered to be 75 per cent) Urea clearance subsequently was determined on 75 occasions in the succeeding 27 months Thirty determinations were obtained by standard clearance with urine volumes never less t'

and 45 by maximum clearance with urine volumes varying from 2.1 to 9.2 cc per minute Urea clearance was below 75 per cent on 10 occasions and within the normal range of 75 to 150 per cent on 65 The two final clearances of 75 and 80 per cent after administration of 33 000 Gm alkali, duplicated exactly the values obtained before alkali therapy

The blood urea nitrogen remained normal throughout the entire study Results ranged from 8.2 to 16.5 mg per cent with an average of 11 to 12 mg per cent

The authors attribute the remarkable tolerance to sodium bicarbonate in their case to the excellent function and reserve capacity of the kidney as well as to the large volume of fluid available for excretion of alkali Absence of demonstrable renal injury after administration of massive quantities of sodium bicarbonate is in accord with recent clinical observations indicating that alkalis per se do not cause intrinsic renal disease

[These observations are proof of the fact that the human organism can tolerate large doses of earthy alkalis or systemic antac Is if the renal system and I might add the hepat c is in tact A certain number of physicians treat themselves and their ulcer bearing patients exclusively with sodium b ca bonate While it is true that the carbonates of sodium and calcium in small dosa e afford inexpensive and prompt relief as a rule they do g e rise to alkalosis in a certain percentage of patients if used in large amounts without proper safeguards —Ed]

Value of Sodium Chloride in Prevention of Alkalosis during Sippy Treatment with Calcium Carbonate Joseph B Kirsner and Walter Lincoln Palmer[6] (Univ of Chicago) report that alkalosis complicating Sippy treatment with calcium carbonate can usually be prevented by concurrent administration of adequate amounts of sodium chloride In 150 patients with peptic ulcer such combined therapy decreased the incidence of alkalosis from 30 to 10 per cent The daily intake of sodium chloride (in addition to the salt in the diet) of the patients in whom alkalosis did not develop averaged 4.5 Gm for 61 patients and 5.10 Gm for 74 The daily intake of the 15 patients in whom alkalosis developed averaged 3.5 Gm for 7 patients and 5.10 Gm for 8

This type of alkalosis is due to chloride loss attendant on gastric aspiration The therapeutic action of sodium chloride is probably attributable (1) to replacement of chloride ion lost by aspiration of gastric contents and (2) to increased excretion of base bicarbonate in the urine at the expense of the blood bicarbonate after administration of salt The experimental observations of Schoenthal are significant in this connection Hartmann and Smyth had shown previously that in the presence of an increased level of plasma bicarbonate secondary to loss of chloride administration of sodium chloride leads to excretion of bicarbonate in the urine Schoenthal gave six healthy infants 6 10 Gm sodium chloride daily, distributed equally in the feedings over one to four days A 6 15 per cent increase in chloride concentration of the serum was observed in all infants The plasma bicarbonate decreased moderately in four infants and the reaction of the plasma of three infants tended to shift toward the acid side The excretion of base bicarbonate in the urine was usually increased and accompanied by a rise in pH There was naturally an increase in the urinary chloride but this did not equal the intake *These data are in agreement with the observations of* Gyorgy in his study of excretion of acid by infants after administration of sodium chloride

In several patients of the present series sodium chloride therapy was apparently not only inadequate to forestall development of alkalosis but insufficient to correct acid base disturbance It is possible that insufficient amounts of salt were given to these few patients and also that excretion of bicarbonate in the urine was retarded by antecedent impairment of renal function

Efficacy of the Drip Method in Reduction of Gastric Acidity Albert Cornell Franklin Hollander and Asher Winkelstein[7] (*Mount Sinai Hosp New York City*) present a quantitative study of the relative merits and efficacy of milk $NaHCO_3$ aluminum hydroxide gel and

(7) Am J Digest Dis 9 332 338 Octob[illegible]

aluminum phosphate gel as determined by observa tions on 38 patients with peptic ulcer All three prep arations were found to be efficient intragastric neutral izing agents when administered by the continuous drip method In the treatment of 34 patients with gastric and duodenal ulcers without obstruction both alumi num phosphate and milk $NaHCO_3$ maintained an aver age intragastric pH of about 4 0 aluminum hydroxide was somewhat less efficient with a mean pH around 3 5 which is nevertheless the boundary value for 'no free acid Neither the milk $NaHCO_3$ nor the aluminum hydroxide gel was effective to any considerable degree in four cases of pyloric obstruction

The percentages of individual samples with pH greater than 3 5 likewise afford good measure of the relative number of times when free acidity was com pletely absent or neutralized In control tests on the 34 patients without obstruction free acid was absent in only about 1 per cent of the samples with milk mix tures and aluminum hydroxide gel this occurred in about 53 per cent and with aluminum phosphate in about 60 per cent If less rigorous specifications for re duction of acidity i e pH 2 0 (10 mN) are accepted as a suitable criterion of adequate neutralization then the milk drip was effective 75 per cent the hydroxide 83 per cent and the phosphate 97 per cent of the time in contradistinction to 11 per cent for the untreated control tests

None of these procedures succeeded in maintaining the stomach free of acid throughout treatment On the other hand the proportion of high pH values as well as the mean pH s indicates considerable efficiency in acidity reduction Both these values may be consider ably increased by increasing the concentration of ant acid in the drip fluid and by elevating the rate of flow above that used in this series The apparent antacid superiority of the phosphate gel over the aluminum hydroxide and milk $NaHCO_3$ as used here may be due) use of the aluminum phosphate without dilution

[The superiority of the drip method over conventional procedures is unquestionable especially in the treatment of the more refractory lesions such as jejunal ulcer When intubation is not well tolerated nocturnal feedings at 1 00 and at 2 00 and 4 00 a m for as long as circumstances dictate have proved effective —Ed]

A Sensitive and Specific Procedure Suitable for Clinical Purposes of Detection of Blood in Urine, Feces and Gastric Juice with Use of the Spectroscopic Method is described by R Eder and Chr v Lippert[8] (Zurich) Attention is called to references in the recent literature concerning the imperfect specificity of the peroxidase reaction for detection of blood in urine feces and gastric juice The customary procedure of increasing the specificity of the peroxidase reaction by use of a glacial acetic acid ether extract of the material being tested carries with it the risk that the iron containing pigment of the blood can be destroyed by peroxide present in the ether

The authors have devised a method with which the sensitivity of spectroscopic detection of blood pigments is considerably increased over that with previous methods The blood pigment is extracted by shaking with a comparatively small volume of carbon tetrachloride or trichlorethylene and the emulsion thus formed is clarified by centrifugation After concentration of the carbon tetrachloride or trichlorethylene extract the retained blood pigment is dissolved in the smallest possible volume of a pyridine hydrazine mixture By this means a relatively high concentration of the blood pigment is obtained for spectroscopic analysis

This principle has been applied in development of a sensitive and specific test for blood in urine feces and gastric juice The procedure for testing urine is described

TECHNIC —About 250 cc urine is mixed with 50 cc pure glacial acetic acid This is shaken in a separatory funnel (500 cc) with 10 cc carbon tetrachloride as thoroughly as possible for five minutes It is allowed to stand for 10 minutes while the carbon tetrachloride layer separates as the lower layer into a milky emulsion This is centrifuged for 10 [illegible] in a high

(8) Schweiz med Wchnsch 1 451 [illegible]

speed centrifuge With most urines centrifugation results in formation of a firm mucous cake so that the supernatant urine can easily be poured off A still better separation is produced if the carbon tetrachloride solution with its mucous cake is shaken with some additional carbon tetrachloride in the cen trifuge tube and then recentrifuged The cake can then be pierced with a small glass tube and lifted out of the cen trifuge tube as a whole The completely clear carbon tetra chloride solution is poured into a small Erlenmeyer flask (10 cc) and with steam suction evaporated to dryness on a hot plate with care to avoid overheating of the residue Finally 5 drops of the pyridine hydrazine reagent (solution of 1 to 2 drops hydrazine hydrate in 5 cc pure pyridine) is used to dissolve the residue and this is poured into an optic tube The material remaining in the flask is dissolved in an ad ditional 5 drops of the pyridine hydrazine reagent and also poured into the tube to be used in the spectroscope

This technic makes possible the detection of 1/100 drop of oxalated blood (about 1/2 000 cm) in 250 cc of blood free urine which indicates a dilution of 1 500 000

The practical value of the test was proved in in vestigation of 57 urine specimens Early fears that per haps the test would always give a positive reaction were not corroborated by this study for 31 of the 57 specimens displayed a completely negative reaction

[Authorities at home and abroad place considerable reliance on the results of occult blood tests of the fec s When one realizes that negat ve reactions may be obtained in individuals pa taking of th ir daily quota of meat the necessity for more reliable m thods is apparent —Ed]

The Effect of Aspirin on the Gastric Mucosa as de termined by gastroscopic examination is described by William D Paul[9] (State Univ of Iowa) Four groups of patients were studied Group 1 included 160 patients with gastro intestinal symptoms but negative roent genograms and 22 with proved duodenal ulcer group 2 27 patients with a benign ulcer on the lesser curva ture group 3 12 patients with a vague history of dys pepsia or distress and negative laboratory findings and group 4 7 patients who had been taking aspirin for many years and 2 who had epigastric distress after in gestion of aspirin All patients were given 10 15 gr aspirin before examination except those in group 3

who received 50 80 gr during the 24 hour period preceding examination These patients were also examined before and after ingestion of aspirin to determine the previous existence or persistence of any changes which might be attributed to the drug

The results indicate that aspirin does not produce hyperemia or hemorrhages in the gastric mucosa even in doses as high as 80 gr per day Furthermore those who had been taking the drug over long periods showed no evidence of chronic gastritis arising from habituation Therefore the epigastric distress which sometimes occurs after ingestion of aspirin may be the result of increased acid production and pylorospasm

[These observations anent aspirin are in direct contrast to those published by Douthwaite and Lintott (1938) and reviewed in the 1939 YEAR BOOK OF GENERAL MEDICINE p 681 Paul s observations are reassuring but I am still going to be circumspect about the use of aspirin in my patients with gastroduodenal disorders. When generous doses of the drug are necessary calcium gluconate or some antacid should be added.—Ed]

Aerophagia G Hoyme[1] (Eau Claire Wis) states that many conditions are associated with abdominal fulness gas and belching and that these symptoms may be elicited or intensified by aerophagia a self induced method for so called removal of 'gas' This is a frequent finding in various gastro intestinal lesions such as gallbladder disease and most notably functional or irritable colon Cardiac irregularities coronary disease and renal and even pelvic disease are conducive to aerophagia

The mechanism of aerophagia is best demonstrated fluoroscopically by a veteran belcher with a glass of barium Initially there are observed small air bubbles which follow each other down the esophagus to form the usual gastric air bubble Then as the patient is instructed to rid himself of the 'gas action ensues A sucking act starts extra large air bubbles on their downward course These inflate the stomach to an astounding degree often to twice the amount of ingested barium Usually after the fifth or

(1) Mi n ota M d "8 350 35" April, 19

released and personal satisfaction as to sound effect volume of released gas and relief is accomplished

Inflation of the stomach in this manner is associated with epigastric fulness pain and dyspnea to the point where the patient wonders where the next breath is coming from Palpitation and premature contractions may be experienced Such gastric distention also causes marked embarrassment to a decompensated heart with symptoms such as vertigo hazy vision dull headache fulness in the head numbness and tingling Heartburn is noted because of regurgitated stomach contents

Deflation brings temporary but grateful relief usually for half an hour whereupon the sensation of gas on the stomach returns and with it persistent belching The false feeling of relief arising from relaxation of the overdistended muscular wall of the viscus encourages repetition of this illogical procedure When air thus introduced is not expelled via the mouth it enters the small intestine and by peristalsis is propelled to the colon with consequent colicky pain

Successful treatment requires thorough search for the underlying cause and its correction Of significance also is the careful explanation of the mechanism of aerophagia augmented by its graphic description Belching is a habit and treatment is further enhanced by instructing the patient to take five or six deep breaths instead of belching Sedatives and heat to the epigastrium are indispensable

Effectiveness of Replacement Therapy in Achlorhydria According to Alfred E Koehler and Emanuel Windsor[2] (Santa Barbara Calif) addition of acid to a representative ground meal at body temperature in vitro shows that the usual amount of acid used in replacement therapy has but little relative effect on the pH *of the meal because of the buffer value of the food* The amount of any acid necessary to bring the pH of a meal to the normal physiologic postmeal range (pH 1 6 1 8) or for peptic activation (below pH 2 0) is of

such magnitude that practical aspects preclude its ad ministration For U S P hydrochloric acid this amount would be 35 cc Even twenty 420 mg capsules glutamic acid hydrochloride with a meal would fail to produce normal acidity or activate pepsin

On acid addition different foods have a buffer or neutralizing effect approximately proportional to their protein content For this reason an average large meal may have 15 20 times the neutralizing ability of the usual Ewald test meal of 3 Gm protein Consequently, evaluation of acid replacement therapy with an Ewald meal may give altogether erroneous results

Except for gelatin the swelling of proteins as a step in solution and digestion is not appreciably influenced by even the largest doses of acid advocated in replace ment therapy In fact the usual doses advocated bring the pH of a meal to minimum swelling of the proteins

Usual acid replacement therapy does not bring the pH sufficiently low to have any appreciable bactericidal effect Certain strains of staphylococci and coli are un influenced by exposure in a meal to the maximum amount of acid therapy practical In fact only com plete attainment of the normal postmeal gastric p" gives anywhere nearly complete bactericidal actio and even this pH may not be effective within the no mal emptying time of the stomach for certain aci resistant encapsulated or sporulated organisms O the other hand certain types of pathogens are ex tremely sensitive to even slight lowering of the pI below neutrality and acid therapy might well be factor in their destruction

Decreasing pH values from 6 5 to 1 5 are instrumen tal in proportionally increased liberation of calcium from milk over a three hour period On the basis of complete equilibrium maximum calcium liberation should occur at the iso electric point of casein pH 4 7 but during a three hour period of incubation complete equilibrium has not been obtained and further lower

ing of the pH results in more rapid liberation of calcium Anacidity or hyperacidity has no effect on thiamine destruction

The amount of hydrochloric acid secreted by the stomach for an average meal must be in excess of 104

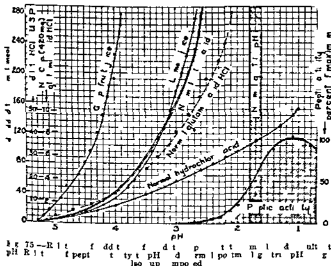


Fig 75.—R l t f dd t f d t p t t m l d ult t pH R l t f pept t ty t pH d rm l po tm l g tri pH g lso up mpo ed

cc normal 35 cc U S P or 3 8 Gm as calculated from the authors data

[With these observations the well informed reader should essentially agree Two facts of practical import might be stated. In achlorhydric states the assimilation of iron preparations is greatly increased by ing t on of 1 drachm dilute hydrochloric acid well diluted and taken during o ght after the meal even smaller amounts of the acid may promptly bring a gastrogenic diarrh a under control —Ed]

Gastroscopic Findings in Anacidity with Special Consideration of Correlation between Clinical Symptoms and Condition of the Mucosa Fifty two patients with histamine refractory achylia were examined gastroscopically by Tage Christiansen[3] (Copenhagen) The mucosa was found to be normal in 12 Superficial gas

(3) G st oe t l gia 67 1 3 131 194

tritis was elicited in 15, atrophic gastritis in 15 hypertrophic gastritis in 7, solitary erosions in 2 and complete atrophy in 1 This indicates that the most common finding in achylia is gastritis In a considerable number of cases however there is no demonstrable anatomic substratum for the anacidity Complete atrophy must be considered extremely rare The condition of the gastric mucosa in anacidity is except for complete atrophy identical with that found in normal acidity and hyperacidity

To study the question of a possible correlation between the clinical symptoms and the condition of the gastric mucosa in anacidity the patients were divided into three groups group 1 12 patients without dyspepsia group 2 23 patients with atypical dyspepsia and group 3 17 patients with a true pyloric syndrome' Whereas both normal mucosa and gastritis were encountered among the patients in groups 1 and 2 in group 3 gastritis was found exclusively It seems therefore that in achylia there is an increase in frequency of gastritis parallel to intensification of clinical symptoms

A Critical Analysis of 938 Gastroscopic Examinations performed on 842 patients is presented by John F Renshaw George E Clark Jr and John R Forsythe[4] (Cleveland) Results of comparison of first roentgen and gastroscopic examinations are given in the accompanying table Gastroscopy was considered to be of value and to have made a significant or major contribution in 217 cases A minor contribution was made in 566 cases and the procedure was a failure in 160 The greatest cause of failure was the inability to visualize the area in question the stoma or large areas of the stomach Other lesser causes in order of frequency were anatomic difficulties, inconclusive or wrong diagnoses poor cooperation technical failure of the instrument and drug reactions The amount of distress suffered was usually not more than that accompanying an Ewald test meal

(4) Am J D ge t Dis 9 401 404 Decembe

Despite its limitations gastroscopy is a valuable diag nostic aid It is indicated in (1) cases of persistent chronic abdominal distress in which gastric disease is suspected even though the roentgen findings are nega tive (2) in cases in which roentgen findings are in determinate or are not consistent with the history and

COMPARISON OF FIRST ROENTGEN AND GASTROSCOPIC EXAMINATIONS

	NORMAL	HYPE TROPI IC GAS THI IS WITH NORMAL OR HYIE RUGAE	U THO OU IO LX M WITH \ R Y CANCER OR ULCER?	ULCER	CANCER	BENIGN TUMOR OR POLYP	STOMA ULCER	TOTAL
Agree	43 (4)	39 (6)		9 (3)	18 (16)			109 (9)
X ray *correct* gastro copic exam. in correct or inconclusive				9 (1)	4 (4)	1 (1)	1	15 (6)
Gastroscop c exam correct x ray incorrect or inconclusive	4		6 (1)	5	/ (4)	1 (1)		3 (6)
Both wrong	1			3 (3)	[illegible] ([illegible])			9 (8)
Both i conclus ve								14

Th figu i p thes ind t a in which th e w surgical or utop y p o f f diagn is

clinical *features* (3) in *cases of gastric ulcer and* (4) in cases of tumor of the stomach except in emaciated persons with obvious clinical and roentgen evidence of carcinoma

[This article is commendable for its conservatism and is a re minder of the important though disconcerting fact that in about a fifth of the cases it is not possible to bring into view the desired area.—Ed.]

Correlation of Gastroscopic and Pathologic Findings in Gastritis Edward B Benedict and Tracy B Mallory[5] (Massachusetts Gen'l Hosp) present a comparative

[5] & Obst 6 1 9 135 F brd ry 1943

gastroscopic and histologic study of 51 cases selected on the basis of completeness of gastroscopic notes and adequacy of histologic material All specimens studied were surgically resected

Superficial gastritis as described by the gastroscopist corresponds to the acute exudative gastritis of the pathologist The term atrophic gastritis is used by both gastroscopist and pathologist to denote the same type of mucosa Hypertrophic gastritis as described gastroscopically corresponds to an exaggerated form of the physiologic plasma cell and lymphocytic infiltration of the normal stomach An extreme form of this is shown in Figure 76



Fig 76 —Gr de IV ntrum Path log ex gg at on of h on c infiltrate u py ng tw th ds of mu × 30

In the 51 cases in this series including all types of gastritis there was complete gastroscopic pathologic agreement in 28 cases (54 9 per cent) and partial agreement in 17 (33 3 per cent) or a total complete or partial agreement of 88 2 per cent There appeared to be no correlation in the six remaining cases (11 8 per cent) Analysis of the separate types of gastritis showed agreement in 74 5 per cent of the hypertrophic 66 7 per cent of the superficial and 66 7 per cent of the atrophic type Such close pathologic verification of the gastroscopic findings in gastritis is an important indication of the value of gastroscopy

Gastroscopy as an Aid to Gastric Diagnosis in the Army is discussed by K Henkel[6] During 1941 1 400 soldiers were examined in the roentgen department of

(6) Münch n med W hnschr p 599 1942

the Air Force Hospital Munich The stomach and duodenum were found roentgenoscopically normal in 41 per cent of cases while gastritis was suspected in 21 5 per cent Roentgen diagnosis was thus unsatisfactory in 62 5 per cent of cases An attempt was made to improve the diagnostic results by use of gastroscopy This method was employed only after all others had been used in 170 cases in all Hypertrophic gastritis was found in 31 per cent of cases edematous catarrhal swelling of the mucosa in 25 per cent atrophic gastritis in 6 5 per cent and gastric ulcers in 4 per cent gastroscopy was unsuccessful in 2 5 per cent A comparison was made of the diagnoses in these 170 cases Roentgen diagnoses consisted of a normal stomach in 45 5 per cent of cases gastritis in 50 per cent and gastric ulcers in 4 5 per cent gastroscopic diagnoses included normal stomach in 31 5 per cent of cases gastritis in 64 per cent and gastric ulcers in 4 5 per cent

Chronic Gastritis Simulating Gastric Carcinoma Eugene Freedman Paul M Glenn and Thomas C Laipply[7] (Western Reserve Univ) report five cases in which diagnostic difficulties were such that carcinoma could not be excluded before exploratory laparotomy was done In three cases the true nature of the lesion did not become apparent until histologic examination of the resected specimens was made

In keeping with the opinion that symptoms of gastritis follow no characteristic pattern the patients in this series had no characteristic complaint except epigastric pain This however varied considerably in degree duration radiation time of occurrence and method of relief In four cases the symptoms were associated with considerable weight loss The only significant abnormalities noted on physical examination were evidence of weight loss and anemia These facts served to enhance the clinical impression of carcinoma

Gastric analyses did not yield uniform results The stools contained occult blood in three of four cases so

(7) A h I t M d 71 23 37 J ry 1943

examined The most uniform finding was hypochromic anemia, which undoubtedly resulted from blood loss The authors direct attention to the observation that severe gastritides may, like carcinoma, be associated with gross hemorrhage

From the roentgenologic standpoint the cases reported *emphasize the necessity of care before a diagnosis* of carcinoma of the stomach is made According to Berg gastritis is differentiated from carcinoma either by generalized distribution of widened rugae rearranged in a mosaic like pattern throughout the entire stomach or by its less frequent localization in the pyloric end Defects produced by polypoid gastritis may be circular He also states that chronic gastritis produces intraluminary defects, with occasional roughening and a 'toothed contour of the side of the greater curvature but without marked changes in the contour of the whole stomach According to Berg peristaltic waves usually traverse the involved area without *interference*

The reported cases however demonstrate that chronic gastritis if localized is not necessarily limited to the pyloric portion of the stomach In one case it was situated on the side of the greater curvature and in two others only the cardiac portion was involved In three of these cases chronic gastritis had led to rigidity of the wall with absence of peristaltic waves and marked deformities of the contour Pyloric obstruction was present in one case

If the wide and irregularly arranged linear or polypoid rugae are associated with defects of contour the roentgenologic differentiation between gastritis and carcinoma may be difficult or impossible In such instances repeated examinations at short intervals may show some regression in the changes favoring gastritis

In each of these cases there was involvement of all coats of th stomach The mucosa was in all instances involved and increased rather than

ness In most of them varying degrees of acute and sub acute inflammation were superimposed on the more marked chronic process

In addition to the gastritis one case exhibited carci noma limited to the mucosa Such carcinoma in situ is not an outspoken invasive tumor but it can be consid ered a type of preinvasive carcinoma of the stomach The time at which invasion may begin is of course problematic The simultaneous occurrence of chronic gastritis and this noninvasive carcinoma may indicate a relationship between the two There is a stage in the development of every large carcinoma in which there are only a few malignant cells in the mucosa. Carci noma in situ is thought to be such a lesion It might thus be the intermediate stage between chronic inflam mation of the stomach and outspoken gastric carci noma

Patients with chronic gastritis should therefore be carefully followed with repeated roentgen and gastro- scopic examinations to discover if possible gastric carcinoma in its early stage and thus increase the per centage of surgical cures of carcinoma of the stomach

[Routine recourse to gastroscopic examinat on in all susp cious cases when the roentgenologic findings are negative or inconclu sive often leads to the visualization of what appears to be a more or less localized area of gastritis On subsequent examination, areas of ulceration strongly suggesting carcinoma appear and if of sufficient depth can then be recognized roentgenoscop cally By this procedure carcinoma in its earl est stages is occasionally encountered. The causal role of gastritis to such mal gnancy is still a controversial matter —Ed]

Chronic Gastritis Its Relation to Gastric and Duo denal Ulcer and to Gastric Carcinoma Robert Hebbel[8] (Univ of Minnesota) describes the manifestations of chronic gastritis encountered in 260 stomachs obtained at autopsy in 106 stomachs resected for duodenal or gastric ulcer and in 52 stomachs resected for carci noma Stigmas of gastritis were searched for in each specimen and findings were recorded separately for the antrum and body Onlv the principal anatomic features

(8) —Am J P th 19 43 71 J u ry 1943

gastritis was exhibited by 30 per cent of the 108 pa tients past 50 This form of gastritis is unimportant in resected stomachs from persons under 50

Among the 106 stomachs resected for ulcer (78 duo denal 13 gastric and duodenal 15 gastric) there was an antral gastritis in all 98 cases in which the antrum

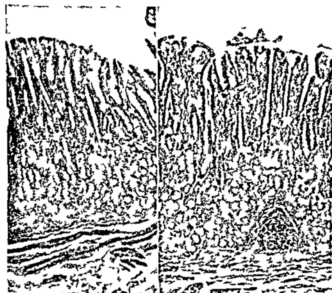


Fig 79 (l ft) —N m l nt l mu Hem t xyl eo d ed f m × 75

Fig 80 (right) —A t l mu M ld lymph yt nfilt t n d ngl lymph id f llicl gland tact H m toxyl d d f m × 75

was examined Changes in the body mucosa were rare in the duodenal ulcer group and common in the gastric ulcer group The evidence substantiates the contention that an antral gastritis (and duodenitis) precedes and is the anatomic basis for the development of chronic ulcer

Gastritic changes encountered in 52 resected carci noma bearing stomachs were variable in extent and severity Al ough numbers of these stomachs pre

of chronic gastritis were recorded viz, lymphocytic and plasma cell infiltration lymph follicles atrophy of glands metaplasia to an intestinal mucosal pattern and for the body mucosa the pseudopyloric glands The degree of change for each of these features was arbitrarily graded 1 3 and the specimens were divided into

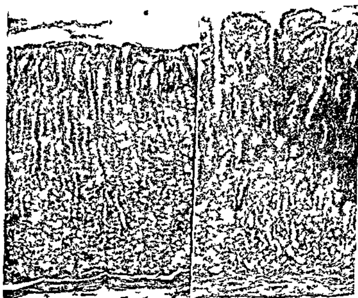


Fig 77 (left) —Normal body mucosa H matoxyl n-eosin reduced from × 75
Fig 78 (ght) —B dy mucosa showing mod ate lymphocyt c infiltration a d at phy de pened p ts b il parts of gland well r tal d Hematox yl n-eos n educed f m × 75

three groups Illustrative sections are presented in Figures 77 80

The autopsy series included patients of all ages dying from a variety of causes whose histories revealed no evidence of gastric symptoms The changes exhibited by this group were chiefly those of a pangastritis leading to atrophy The process bore no demonstrable relationship to any factor other than age Gastritic changes in any degree were rare under the age of 30 and severe changes were uncommon under 50 Atrophic

and can be directly traced to an area of atrophy to the exclusion of other areas From the very nature of gastric material universally available in large clinics this type of evidence although it may eventually appear will be long in coming Could even this be proved correct the larger question would still remain unanswered as to why A with gastric atrophy gets cancer and B with the same atrophy does not Prematurity in formulating important conclusions in matters of this sort is unjustified

Polyps of the Stomach and Polypoid Gastritis Edmund I Spriggs[1] presents an extensive review of these subjects together with plates illustrating gastroscopic histologic and roentgenographic findings

Polyps of the stomach may consist of papillomas adenomas or leiomyomas Diagnosis is made by either roentgenographic or gastroscopic methods Spriggs reports 10 cases diagnosed during roentgen examination of 4 424 patients in an eleventh case a duodenal polyp was revealed by operation During this period there were 104 cases of gastric malignancy and 570 of peptic ulcer

Similar symptoms occur from polyps of varying pathologic nature There is little or no change in the movements of the stomach unless the pylorus is obstructed Small tumors away from the pylorus may be asymptomatic The presence of multiple polyps may also be unattended by symptoms but not as a rule Symptoms are usually those of dyspepsia particularly if prolapse into the pylorus has occurred If the tumor becomes necrotic or ulcerated gross hemorrhage or silent bleeding with secondary anemia may occur Dyspeptic and hemorrhagic symptoms may exist concomitantly Gross hemorrhage is suggestive of either leiomyoma or polyposis

Partial or subtotal gastrectomy is the procedure of choice particularly if the polyp is large or if hemorrhage or persistent dyspepsia occurs Polyps are prone

(1) [illegible] Med 12 1 60 J[illegible]ry 1943

sented a diffuse atrophic gastritis which undoubtedly antedated the tumors that condition did not obtain for all In a few instances the body mucosa was normal or nearly normal In others, although there were severe changes in the vicinity of the tumor, the more distant portions of the excised segments were less, or not at all affected The findings in such cases suggested that the mucosal changes were secondary to the tumor al though the possibility of the coincidental association of the tumor and a developing atrophic gastritis could not be excluded There was in this series no evidence to indicate that carcinomas arise with unusual fre quency in stomachs already the seat of a diffuse atrophic gastritis

Chronic Atrophic Gastritis and Cancer of the Stom ach The often reiterated claim that chronic atrophic gastritis is a precancerous lesion has received no posi tive support from an extensive study conducted by Lewis W Guiss and Fred W Stewart[9] (Memorial Hosp, New York City) The slight difference in inci dence of gastric atrophy between cancerous and non cancerous stomachs in the large series studied is far from convincing Atrophic gastritis is an exceedingly common condition with advancing age Mere statistical correlation of incidence of gastric atrophy and cancer is insufficient to show causal relation Both atrophy and cancer appear to be events in aging organs Were the effort made it would doubtless be easy to show that gastric cancer was correlated not only with gastric atrophy but likewise with atrophy of other organs even in fact with atrophy of such anatomically unre lated structures as the genitalia, breasts circulatory apparatus or skin thus reducing to absurdity the con clusions based on mere statistics as evidence

To assert on morphologic grounds that the origin of gastric cancer depends on the existence of gastric atrophy would require far more evidence It would at least require proof that early gastric cancer begins in

(9) Arch Surg 46 823 848 June 1943

Benign Submucosal Tumors of the Stomach Gastroscopic Study The diagnosis of benign submucosal gastric tumors and their differentiation from benign mucosal tumors are possible by gastroscopic examination Small submucosal tumors do not become clinically important until they protrude the gastric mucosa all tend to ulcerate and bleed

Symptoms are often only syncope weakness fatigue and palpitation with secondary anemia Gross hemorrhage in the form of hematemesis or tarry stools is the chief symptom One sign not compatible with a mucosal tumor and permitting the diagnosis of a submucosal variety is the stretching of a mucosal fold from the surrounding mucosa up to the surface of the tumor apparently bridging the space between the top of the tumor and the level of the surrounding mucosa



Fig 8 —Sam p ed g G oss pe m f t m pe t n lmost th y rs fte g t py Ulc r tio t t p of t m pr b bly dev loped da g th t m t t hi g f fold not w ll h w

Rudolph Schindler (Chicago) David J Sandweiss (Detroit) and I Lew Mintz (Los Angeles) report three cases in only the third reported here was diagnosis proved by surgery and microscopic study

Man 53 s en Mar 30 1936 had intermittent attacks of heartburn nausea and a heavy feeling in the epigastrium after meals Examination gave negative results except for free hydrochloric acid in the gastric contents With a bland diet pain disappeared On December 20 the patient complained of acut pain weakness dizziness and tarry stools As a

(2) Am J Dig t Dis 9 39 9 September 194

to malignancy, however, they may exist for years without causing mishap as was demonstrated in six persons who were poor operative risks

Polypoid hyperplastic swellings of the gastric mucosa were observed in 19 cases in 7 of which there was a gastro enterostomy opening or past or present peptic ulceration In 3 of the remaining 12 cases there was evidence of excessive use of alcohol Swallowed septic material was an obvious cause in one and a probable cause in two others During the same *period a diagnosis of gastritis* was made in 470 cases All of the 19 patients *complained of dyspepsia with an inconstant food relation*



Fig 81 —Gastroscopic picture of typical submucosal benign tumor Benignity apparent from smooth surface and entirely sharp limitation submucosal location s d gn d f m many stretched-out folds bridging r ces ion of tumor Antrum and pylorus seen in right upper quadrant Diagnosis was confirmed at operation (Schindler et al p 649)

In the patients with peptic ulceration free hydrochloric acid was usually *present in the gastric* juice Histologically the gastric epithelium of those with hyperacidity differed from that of those with hypoacidity or anacidity *the latter showing much degenerative change In nearly all patients without ulceration* free hydrochloric acid was absent or low In three patients progress toward achlorhydria was noted over two to five years and was compatible with clinical improvement Malignancy was not *observed* in any case

Swellings and symptoms subsided in most of these cases after treatment consisting of dietary regulation and repeated gastric lavage

[To those particularly interested this extensive beautifully illustrated article and that by the American authors H Brunn and F L Pearl (*Surgery Gynecology and Obstetrics* 76 257 281 March 1943) should be read in their entirety —Ed]

cause of the frequency of malignant changes in benign gastric lesions surgical exploration and removal of the tumor should not be delayed

Woman 35, had had persistent diarrhea for about 14 months, with three to six stools during the day and two to four stools at night The stools were always watery and oc asion ally contained mucus Once she passed bright red blood with her stool Her appetite remained excellent

Examination disclosed only moderate weight loss Blood studies revealed slight anemia The stools were positive for occult blood on three occasions but negative for parasites and ova Barium studies showed a smooth polypoid structure ex



F g 83 (l ft) — P lyp d fill g d f t tl d w th b rium
F g 84 (ght) —E c ed p lyp

tending from the greater curvature at about its midpoint into the lumen of the stomach (Fig 83) The polyp was almost egg sized and was freely movable except at its point of attachment along the greater curvature The stomach was otherwise not unusual Roentgen interpretation was solitary benign polyp of the stomach Sigmoidoscopic examination was negative Gas troscopic examination disclosed a mass bulging into the lumen of the stomach just above the angulus on the greater curvature It was redder than the surrounding mucosa The surface was somewhat irregular Gastroscopic interpretation favored grade I carcinoma

Examination after surgical removal disclosed a papilloma weighing about 15 Gm and measuring 5 × 4 × 2 cm (Fig 84) Microscopically it was a papillary adenoma of the stom ach with marked chronic inflammatory changes throughout the stalk and considerable ulcerations on the surface There was no evidence of malignancy The postoperative course was un

Sippy regimen did not entirely relieve distress, gastroscopy was done Feb 20, 1937 (Fig 81) A benign submucosal tumor covered with smooth mucous membrane was seen above the angulus Permission for surgery was refused In December 1939, the patient had a hemorrhage which could not be stopped by ordinary therapy surgery was resorted to In January, 1940, a benign submucosal tumor 3 5 cm in diameter (Fig 8?) was removed by subtotal gastric resection There was deep ulceration at the summit of the protuberance

Diagnostic differentiation therefore, is of utmost importance in these cases since submucosal benign tumors tend to bleed profusely and may even prove fatal They should be removed as soon as diagnosis has been established

A Case of Benign Gastric Polyp Producing a Gastrogenic Diarrhea is presented by Gordon J Culver, Walter Westinghouse and E C Koenig[3] (Buffalo) Benign gastric tumors represent only about 0 6 per cent of all gastric lesions Their commonest symptoms include dyspepsia diarrhea anemia and hematemesis Nausea and vomiting are uncommon The chief obstacles to clinical diagnosis are the rarity of the lesion and the vague symptomatology Probably the combination of roentgen and gastroscopic examinations followed by surgical exploration offers the most accurate and logical method of establishing diagnosis

With careful fluoroscopic examination the percentage of correct roentgen diagnoses should be high This is particularly true of pedunculated growths which are usually freely movable and have easily distinguishable pedicles There is absence of infiltration or rigidity of the surrounding gastric wall and the growth does not usually show areas of ulceration as seen in malignant lesions In benign nonpedunculated growths involving the stomach wall diagnosis is difficult, and usually a roentgen diagnosis of a malignant lesion is made Gastroscopic visualization is a valuable diagnostic aid Surgical exploration with pathologic examination of the specimen is the absolute method of final diagnosis Be

(3) Ann I t M d 17 1015 10 0 D eml

accompanied by blushing of the mucous membrane and vigorous contractions of the stomach wall Emotions such as fear and sadness which involved a feeling of withdrawal were accompanied by pallor of the gastric mucosa and inhibition of acid secretion and contractions This complex was encountered infrequently Anxiety hostility and resentment were accompanied by accelerated acid secretion hypermotility hyperemia and engorgement of the gastric mucosa resembling hypertrophic gastritis This series of events was much more commonly observed and was associated with gastro intestinal complaints such as heartburn and abdominal pain Intense sustained anxiety hostility and resentment were accompanied by severe prolonged engorgement hypermotility and hypersecretion in the stomach In this state mucosal erosions and hemorrhages were readily induced by even the most trifling traumas and frequently bleeding points appeared spontaneously as a result of vigorous contractions of the stomach wall Contact of acid gastric juice with such a small eroded surface in the mucous membrane resulted in accelerated secretion of acid and further engorgement of the whole mucosa Prolonged exposure of such a lesion to acid gastric juice resulted in formation of a chronic ulcer The stomach lining was found to be protected from its secretions by an efficient insulating layer of mucus enabling most of the small erosions to heal promptly within a few hours Lack of such protective mechanism in the duodenal cap may explain the higher incidence of chronic ulceration in this region

It appears likely that the chain of events which begins with anxiety and conflict and their associated overactivity of the stomach and ends with hemorrhage or perforation is that which is involved in the natural history of peptic ulcer in human beings

[Verily th modern Beaumonts This is one of the most convincing p eces of research concern d with ulcer genesis in all recorded literatu e —Ed]

Evidence of the Genesis of Peptic Ulcer in Man Stewart Wolf and Harold G Wolff[4] (New York City) undertook to discover some stimulus which causes definite sustained acceleration of acid production and which may be recurrent in the ordinary course of life



Fig 8 (top left) —Normal mu os l f lds t al z
Fig 86 (t p r ght) —Eng g m t of mu o w th motio al co fl ct tual s
Fig 87 (b tt m l ft) —Muc al e os on actual s ze
Fig 88 (bottom right) — I u h d ut ul r ulti g f om prol nged c nta t f ga t c jui w th e of mu o nad q at ly p ot cted by mucus a tu l i e

in ulcer patients A patient with a large gastric fistula whose mucosa was readily visible was studied with regard to possible genesis and tissue damage Acid in small amounts was continuously elaborated under basal conditions Spontaneous transitory phases of accelerated acid secretion occurred from time to time

(4) J A M A 120 670 6 5 O 1 31 194

milk and a biscuit milk feeds during the night if the patient is awake and one third normal saline as desired between feeds on the first day

Morphine was given on admission and whenever further bleeding occurred When melena had ceased 3 gr fersolate and 200 mg ascorbic acid were given three times a day for five days Antacids were not given routinely but calcium and magnesium tribasic phosphate was allowed for pain Laparotomy for arrest of hemorrhage was undertaken on only three occasions but partial gastrectomy or gastro enterostomy was performed during convalescence if indicated

[This article properly emphasizes the rôle of acute gastric le ions in roentgenolog cally negative patients with gross hemorrhages from the upper digestive tract —Ed]

Traumatic Gastroduodenal Ulcers Claude Verdan[6] (Lausanne) states that gastroduodenal ulcers may be caused by internal trauma as chemical or physical burns or swallowed glass or by external trauma as a gunshot wound blow or indirectly a fall Force may be transmitted to the stomach through the ligaments with a full stomach transmission may be hydrodynamic Cutaneous burns plumbism and general septic conditions may provoke lesions of the gastric wall which however heal quickly

The more the problem is studied the less correlation can be found between chronic peptic ulcer and trauma The patient with chronic peptic ulcer presents a characteristic pain syndrome and gastric dysfunction resulting from vegetative nervous system disharmony Traumatic ulcers develop in a mucosal wound which is transformed into an ulcer Legally it is difficult to attribute an ulcer to trauma It is not enough to show it exists but that trauma can cause a gastric lesion capable of becoming chronic The question arises whether trauma merely aggravates a pre existing ulcer Verdan believes that trauma can in certain conditions provoke formation of ulcer and create a gastric lesion capable of passing to the chronic stage but it has not

(6) [illegible] t l g 67 1 9 1942

Hematemesis and Melena F Averv Jones[5] presents an analysis of 171 cases of hematemesis and/or melena treated by prompt feeding and liberal transfusions There were 17 deaths Peptic ulceration was the probable cause of hemorrhage in 161 cases, among which there were 14 deaths Gastroscopy was performed within a week or less in 38 of 51 cases which could not be diagnosed by clinical or radiologic methods In 21 of these cases an acute gastric ulcer was found and in 2 acute gastritis Thus in nearly two thirds of the cases in which other methods failed gastroscopy provided a diagnosis

Treatment was along the general principles described by Witts A drip blood transfusion at 40 drops a minute was begun if it was thought that further bleeding might endanger life If anoxemia became evident, transfusion was accelerated and oxygen was administered at 6 L per minute with a B L B mask In general most patients were given a transfusion if the pulse stayed above 120 per minute if the blood pressure fell below 90 mm Hg or if the hemoglobin reached 40 per cent Transfusions were liberal and usually 1 050 cc was given being repeated if necessary One third normal saline was given to allay thirst Puréed feedings were given at two hour intervals These were usually well taken but occasionally milk feeds would be given if desired

The purée diet was given as follows 6 00 a m a cup of milky tea 8 00 a m porridge and bemax, thin bread and butter marmalade and a cup of milky tea, 10 00 a m a cup of milk and a biscuit noon, minced meat chicken or steamed fish mashed potato and puréed carrot or cauliflower 2 00 p m, egg custard or cereal pudding or apple puree and orange juice 4 00 p m a cup of milky tea three thin slices of bread and butter, bramble jelly and sponge cake 6 00 p m vegetable soup or a minced chicken sandwich 8 00 p m milk pudding or a cup of milk, 10 00 p cup of

(5) Brit M J 1 689 691 Ja 45 1943

milk and a biscuit milk feeds during the night if the patient is awake and one third normal saline as desired between feeds on the first day

Morphine was given on admission and whenever further bleeding occurred When melena had ceased 3 gr fersolate and 200 mg ascorbic acid were given three times a day for five days Antacids were not given routinely but calcium and magnesium tribasic phosphate was allowed for pain Laparotomy for arrest of hemorrhage was undertaken on only three occasions but partial gastrectomy or gastro enterostomy was performed during convalescence if indicated

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been proved that this ulcer can be compared with the round ulcer of Cruveilhier

Conditions for legal acceptance of relation between trauma and ulcer are (1) Patient must never have had dyspepsia before the accident (2) Trauma must have been violent and (3) must have occurred directly to the stomach (4) It must have been followed by immediate objective symptoms such as syncope or hemorrhage (5) There must be bridging symptoms between the accident and present condition of the patient (6) X ray must show gastric lesion

Relationship between post traumatic jacksonian epilepsy and gastroduodenal ulcer has been shown by Kalk and Cushing observed ulcers of the stomach duodenum and esophagus immediately after trephining for cerebral tumors In Kalk s case 15 17 years elapsed before appearance of the ulcer He stated that epileptics frequently have gastric ulcer because epileptic crisis provokes excitation of nervous vegetative centers leading to muscular cramps and augmentation of gastric secretion and formation of ulcers is favored by true gastritis provoked by constant luminal medication

Cutaneous burns are recognized in accident insurance as cause of post traumatic ulceration if it appears during treatment of the burn Septic pyemia may cause submucous abscesses which perforate into the gastric cavity forming fatal ulcers Plumbism is legally recognized as the cause of ulcer when the ulcer is manifested during the period of poisoning such ulcers have been diagnosed six months later

The two principal traumatic aggravations of preexisting ulcer arise from perforation and hemorrhage Perforation *not related* to trauma may occur on unusual effort which may also be the cause of hemorrhage However if hemorrhage is observed immediately after accident the latter may be regarded as the cause

[The factor of trauma especially nonpenetrating external trauma *in the genesis of acute and chronic ulce*[illegible] subject of contention for many years Judging [illegible]

ported traumatic ulcer for anatomic reasons is much more likely to occur in the stomach than in the duodenum The subject is one of increasing medicolegal importance but proof of relationship is extremely difficult Too often in my judgment trauma is only the activator of a pre existing latent lesion —Ed.]

Peritoneal Fluid and Gastric Contents in Cases of Perforated Peptic Ulcer Charles M Henry[7] (Wayne Univ) studied patients with benign ulcers of the stomach or duodenum with free perforation into the general peritoneal cavity and found bacterial infection of the peritoneal cavity a major cause of death with perforation of a peptic ulcer Micro organisms are present in the peritoneal cavity soon after perforation Gastric acidity is low at the time of perforation and bacteria are found in the gastric contents The peritoneal fluid obtained at operation on patients with perforation has a pH and a chloride content approaching that of blood plasma

Diagnosis of Large Gastric Ulcers and Implications as to Treatment Some have long held that every gastric ulcer should be viewed critically and that ulcers larger than a quarter are particularly prone to be malignant This view has been but slowly accepted and even today many patients have cancer of the stomach because for months they were treated on the assumption that any crater like lesion seen in the stomach should be considered benign until proved otherwise

To emphasize the significance of this concept Frederick Steigmann[8] (Cook County Hosp) reports conclusions derived from a study of over 200 large gastric ulcers Results of this study have caused the validity of signs and symptoms thought by some to be typical of benign or malignant lesions to be questioned Even the progress and clinical course in a case of large gastric ulcer are at times unreliable criteria Similarly in determining the nature of a large gastric ulcer no trust can be placed in symptoms signs laboratory tests or x ray or gastroscopic findings Response to medical management is often misleading In some instances

(7) A h S g 45 564 570 Oct be 1942
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even the surgeon and pathologist cannot differentiate a benign from a malignant ulcer, and only histologic examination of the resected lesion will permit exact diagnosis

Roentgen findings presumably are 95 per cent correct in diagnosis of peptic ulcer In cases of large gastric ulcer however, diagnostic errors are made in both directions i e lesions diagnosed as benign by x ray may be malignant and vice versa Similarly, certain

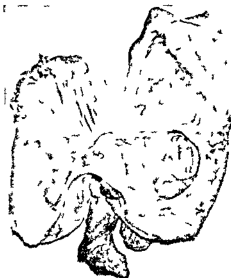


Fig 89 (left) —Large benign gastric ulcer
Fig 90 (right) —Small ulcerating carcinoma

clinical and laboratory data which supposedly point to one or the other type may be fallacious

Current theories in regard to the characteristic symptoms of benign gastric ulcers were reviewed and found incorrect when applied to the diagnosis of large ulcers in this series Long duration is usually assumed to indicate benignity but in this series several patients with histories of indigestion of long duration were shown to have malignant ulcers, conversely gastric symptoms of less than one year s duration obtained in almost 20 per cent of proved large benign gastric ulcers Age was also of little value in differential diagnosis 82 per cent of patients with ben

over 40 while carcinoma with ulcer like niches oc curred in several patients under 40 The type of pain and its response to food alkali or vomiting were of little value since similar complaints were obtained from patients with both types of lesions A large be nign ulcer may invade tissues supplied by the spinal sensory nerves and thereby suggest malignancy



Fg 91—L g be g l h w g p g bl d l wh h led to p t t d th f mm e h m h

Weight loss anorexia and weakness were common in cases of benign ulcer in several cases weight loss ap proaching 40 lb was recorded Hematemesis melena and anemia occurred in both benign and malignant conditions Disappearance of blood in the stool during medical management is supposed to suggest a benign lesion but this occurred in a few cases of malignant ulceration Neither could free acid values above 40 de grees be considered an adequate criterion of benignity

The various x ray signs described as differentiating a

benign from a malignant ulcer refer particularly to the size of the ulcer depth relation to the stomach wall and the rugal pattern location and secondary signs (such as incisura opposite the ulcer, pylorospasm or pain on pressure) Increase or decrease in size are also diagnostic points In cases of large gastric ulcer, how ever most of these points fail as diagnostic criteria mainly because of the distortions that occur in these lesions

The size of the niche is of significance Although some of the largest ulcers are benign some carcinom atous ulcers are rather small (Figs 89 91) Still, a large niche should elicit caution for malignancy mas querades more frequently as a large than as a small gastric ulcer

These observations suggest that every large gastric ulcer should be resected Resection is advisable not only because of the danger of erroneously diagnosing a malignant lesion as benign but also because the com plications of large gastric ulcers make them in a way malignant when they are histologically benign

[On the basis of my own experience I am almost wholly in record with the author s contentions With much justification he has made out a good case for the surgeon in the treatment of the large gastric lesion The internist may weigh the risk of death from gastric resection and that from possible cancer in the indi vidual case The large subacute variety usually responds readily and completely to adequate methods of medical treatment but it is not always possible to distinguish this type satisfactorily before hand —F I]

Significance of Gastroscopic Findings in Patients with Duodenal Ulcer Henry J Tumen and Milton M Lieberthal[9] (Jewish Hosp Philadelphia) studied the gastroscopic findings in 50 cases of duodenal ulcer un complicated by pyloric obstruction to discover what effect the presence or absence of gastritis might have on symp toms and response to treatment of the patient with ulcer Findings were correlated with clinical features

Of the 50 patients studied 33 had chronic gastritis 1 unclassifiable inflammatory changes and 16 normal stom achs Gastritis was superficial in 11 and hic in

(9) Gastroenterology 1 555 564 June 1943

17 atrophic changes were seen in 5 Six of the 16 patients with no evidence of gastritis had an atypical history or poor response to treatment or both While incidence of atypical history and/or poor response to treatment was somewhat greater in ulcer patients who had gastritis than in those who had not it is difficult to ascribe much significance to this because among the 21 patients with gastritis on whom gastroscopy was done more than once clinical severity of symptoms seemed related to the gastroscopic picture in only 10 In the others there was no correlation between the gastroscopic picture and presence or character of symptoms

Presence of gastritis did not regularly influence the clinical course of duodenal ulcer While it is possible in individual cases that gastritis may have added to severity of symptoms gastritis often existed apparently without symptoms

In patients with duodenal ulcer it was impossible to postulate presence or absence of associated gastritis on the basis of the nature of the symptoms or the character of response to treatment This conclusion does not detract from the recognized possibility that gastritis may at times cause severe symptoms both in patients with ulcer and in those without

[The regularity of the symptom complex of uncomplicated duodenal ulcer and the typically favorable response to adequate treatment has been commented on by many authorities Moynihan s well known observation that the diagnosis can be made by correspondence is exemplification of this But the fact remains that at least 15 per cent of such ulcer bearing patients present symptoms lacking in whole or part the familiar pain food ease sequence The factor or factors underlying such irregularity apart from psychoneurosis are intriguing and should be a field for fruitful research Hence the interest in this and similar investigations —Ed]

Duodenal Ulcer Syndrome Caused by Ankylostomiasis H A Yenikomshian and William H Shehadi[1] (American Univ Beirut) present 25 cases of ankylostomiasis in which in addition to routine clinical and laboratory studies gastric juice analysis and roentgen studies of the gastro intestinal tract were made

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alternate feeding and drainage so that the stomach never becomes distended and is gradually decompressed The routine of procedure is followed closely in the early stages of treatment and is varied later in accordance with progress As soon as the presence of obstruction has been determined a Levin tube is introduced into the stomach and its contents are aspirated Orders are then given to introduce through the tube 3 oz of a bland noncurding mixture such as malted milk made with water peptonized milk or in some cases evaporated milk With this is included 1 2 drachms colloidal aluminum hydroxide This mixture is given every hour day and night For the first 30 minutes of each hour the tube is clamped so that no drainage returns For the last 30 minutes of each hour the tube is unclamped and the gastric contents are allowed to drain by siphonage into a bottle attached beside the bed about 1 ft lower than the level of the patient This return drainage is measured and the total 24 hour return is charted as a graph on the temperature chart in the same manner that the fluid intake or output might be charted

The graphic record of the degree of obstruction and its response to management permits quick and accurate decision as to which patients can best be managed medically and which should be treated by operation Finally the latter reach the surgeon in a better state of nourishment with a better fluid balance and with much improved gastric tone as compared with those who have an occasional aspiration or continuous gastric suction for one or two days

Physiologic Basis for Dietotherapy in Duodenal Ulcer is discussed by Harry Shay Jacob Gershon Cohen Samuel S Fels and Herman Siplet[3] (Philadelphia) Diets for this condition are composed of nonirritating foods which do not increase gastric secretion and have a good acid combining power Milk and cream have a beneficial effect in the stomach because of their high acid

(3) J A M A 120 740 74 N 7 1942

Twenty three patients complained of digestive disturbances and abdominal pain In 10 epigastric pain had a definite relation to meals, coming on one to four hours after food ingestion These patients awoke at night with epigastric pain which was relieved by intake of food and alkalis *Small quantities of soft and easily digestible* food relieved the pains while coarse food or large quantities of food increased the discomfort In none of these patients was there vomiting hematemesis or melena. All had relief from epigastric pain and distress within 24 hours after administration of carbon tetrachloride and oil of chenopodium In patients whose pain persisted or returned shortly after administration of the vermifuge it was noted that ova of *Ankylostoma duodenale* were still present in the stools A second dose of vermifuge produced complete relief from symptoms

Estimation of free gastric acidity in this series disclosed a rise to a level higher than that obtained in duodenal ulcer Despite varying degrees of severe anemia this high gastric acidity was maintained Roentgen study in these cases disclosed evidence of swelling of the duodenal mucosa inconstant deformity of the duodenal bulb (duodenitis without ulcer niche) hyperperistalsis of the stomach and duodenum and commonly reversed peristalsis of the duodenum without obstruction These changes were eliminated 11 24 days after administration of the vermifuge

Obstructed Peptic Ulcer S Alan Wilkinson (Lahey Clinic) reviews 100 cases of ulcer with obstruction seen prior to 1936 The ratio of males to females was 3 1 *Obstruction which has persisted over three months is* practically certain to recur although the patient may sometimes go for many years without trouble Obstruction in the female is attended by less hope for medical cure than in the male Most women will need operation.

A simple easily managed procedure for handling pyloric obstruction is presented This consists chiefly of

( ) Am J Digest D s 9 821 3 7 October 194"

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(3) J A M A 1 0 740 742 N 7 1942

neutralizing power After reaching the duodenum largely by action of their fat content they stimulate mechanisms responsible for gastric motor and secretory inhibition and thus help overcome abnormal gastric phenomena seen in uncomplicated duodenal ulcer—hy

Standard water-barium meal 250 cc of water 2 ounces of barium				
Milk barium meal 250 cc AA milk 2 ounces of barium				
Cream barium meal 250 cc of table cream 2 ounces of barium				
Milk -150 drops a minute through duodenal tube standard water-barium meal by mouth				
Cream--60 drops a minute through duodenal tube standard water barium meal by mouth				

Fig 9 —D a i gs to l f m film of n rm l pe Stom h mpt compl tely a 250 c water ba m me l n 60 m n (row 1) W th m lk ub t tuted for wate 30 p t g t c d w f und (w) S b st tut n of t ble c am for milk r sult d n 90 pe e t t m h re d (row 3) Th t ga t m t d l y us d by m lk nd e m dep ls o the r re hing th duodenum was st k ngly d mo t ted by ffe t n g t c empty g wh n th se ge t we nst ll d d tly nto the d od um nd water b ium m al given by m uth (w 4 nd 5) M e st k ng eff ct s seen when cream used 100 per ent ga t c r d e t 60 m n wh n nly 60 drop of m m ute w st ll d into duodenum (row 5) nd sl ght g st c empty g wh n much 150 d p f m lk a m nut wa i t lled int duodenum under s m l nd ti (ow 4)

permotility hyperperistalsis hypersecretion and hyper tonicity In many instances milk alone is not sufficient to stimulate the gastric acid reducing duodenal mech anism Cream however was found in all cases to reduce gastric acid when instilled slowly into the duodenum The duodenal gastric motor mechanism has a lower threshold of response and requires a lesser stimulus than the duodenal gastric secretory mech

even more effective than cream in stimulating gastric motor and secretory control mechanisms on reaching the duodenum

Uncomplicated duodenal ulcers which fail to respond to adequate medical therapy may be those in which the duodenal mechanisms are so obtunded that they fail to react to the usual dietary agents which bring these mechanisms into play when they reach the duodenum

The authors believe that gastric hyperacidity with consequent disturbance of the duodenal mechanisms may be a causative factor in production of duodenal ulcer The sequence of events may well be a disturbance in the duodenal mechanisms in which their threshold is raised resulting in (1) gastric motor changes producing hypermotility and increased evacuation with a consequent increased trauma to the duodenal cap and (2) gastric secretory changes resulting in hypersecretion which further traumatize the duodenal mucosa

Gastrojejunocolic Fistulas With Special Reference to Associated Nutritional Deficiencies and Certain Surgical Aspects are discussed by John S Atwater Hugh R Butt and James T Priestley[4] (Mayo Clinic) Gastrojejunocolic fistula results in a unique mechanical gastro intestinal shunt By its mechanism a decrease occurs in the available absorptive intestinal surface The presence of such a pathologic anatomic pattern is conducive to development of nutritional disturbances

In the authors series of 42 cases with two exceptions gastrojejunocolic fistula followed gastrojejunal ulcer the ulcer having been a sequela to a previous operation usually gastro-enterostomy In 42 per cent of these 40 cases the fistula occurred within a year after the original operation In one case a gastrojejunocolic fistula developed for the second time All patients were males Average age at clinical onset was 45 The estimated incidence of gastrojejunocolic fistula in the presence of gastrojejunal ulcer is 11 14 per cent

Diarrhea and fecal belching or vomiting are the com

(4) An S g 117 414 4 6 Ma ch 1948

monest symptoms Evidence of malnutrition is manifold. Extreme loss of weight and strength and the presence of dehydration emaciation hypoproteinemia nutritional edema anemia and multiple vitamin deficiency states are characteristic Such vitamin deficiencies as night blindness peripheral neuritis paresthesias pellagra, glossitis conjunctivitis cheilosis, ecchymoses with decreased values for blood ascorbic acid and hypoprothrombinemia have been observed. The primary object of preoperative care should be to replenish each of the depleted body nutritional stores and in so doing to restore the patient to satisfactory chemical and physical health, so that surgical operation can be performed with the least possible risk

The surgical treatment of choice is gastric resection after the stomach jejunum and colon have been detached *from their* fistulous connection In certain cases preliminary colostomy may be advisable Operative mortality rate in this series was approximately 27 per cent but this will be materially reduced in the future Results after gastric resection are definitely superior to those which follow mere removal of the fistulous tract in a procedure unassociated with partial gastrectomy

Nonfunctioning Gastro Enteric Stoma is an infrequent late postoperative phenomenon. The preponderance of the condition among males of duodenal ulcer as the original lesion and of primary postoperative gastro enteric hemorrhage and the frequent shift of pain and tenderness to the left abdominal quadrant are clinical features which strongly imply that the causative factor is an ulcerative or inflammatory process involving the anastomosis Such symptoms and signs typified the clinical picture presented by three fourths of the 62 patients studied by *George B Eusterman, B R Kirklin and Carl G Morlock*[3] (Mayo Clinic)

Surgical observations were (1) marginal or jejunal ulcer and gastrojejunitis in 48 patients (2) mechanical conditions such as volvulus and extensive adhesions

(3) Am J Digest. Dis 9 313 317 October

(chiefly involving the loops) in 8, and (3) no surgically demonstrable abnormality of the stoma in 6 the condition being classified as dysfunction

In 90 per cent of the patients who had roentgen evidence of nonfunction, the presence of a demonstrable pathologic process was surgically confirmed

Although a nonfunctioning gastro enteric stoma is associated with the implication of complete gastric obstruc-



Fig 93 —Three types of resections A of pyloric antrum B resection carried proximal to incisura angularis (I A) on lesser curvature and leaving greater portion of greater curvature C of more than two thirds of stomach (Holman McSwain, below)

tion, such obstruction actually is infrequent Forty eight of 60 patients in this series had gastric retention but it was of considerable degree in only one third There was no demonstrable impairment of gastric motor function among 20 per cent of the patients Nonfunction may have occurred when the stoma is found to be patulous on gastroscopic examination or at operation Explanations for disparity between roentgen data and clinical facts in respect to motor function are advanced

Gastric Acidity Following Gastric Resection In reviewing the results of three types of gastric resection Cranston W Holman and Barton McSwain[6] (Cornell Univ) find that removal of the antrum results in reduced acidity or anacidity in only 25 per cent of patients Removal of one half to two thirds of the stomach plus a portion of the lesser curvature proximal to the re entrant angle results in reduced acidity or anacidity in 80 per cent of patients Removal of more than two thirds of the stomach results in reduced acidity or anacidity in 90 per cent of patients The authors conclude

(6) Surgery 13 916 933 … 1943

that many advantages of technic are sacrificed when large portions of the stomach are removed and that little is gained To retain resection as a useful procedure, it is advised that gastric resection be done so as to insure the highest percentage of cases of postoperative anacidity without sacrificing too much of the stomach This can *be done by removing one half to two thirds of the stomach including a portion of the lesser curvature proximal to the re entrant angle and retaining a fair portion of the greater curvature*

Acute Perforations of Malignant Gastric Tumors Garcia Baron[7] reports three cases of rare acute perforations of malignant gastric tumors One patient had a primary carcinoma without history of gastric disturbances perforation was the first symptom The second patient had apparently a carcinomatous ulcer and the third had a sarcoma with a history of hyperacidity, subacute perforation leading to a subphrenic abscess and apparent surgical cure followed in a few months by development of a stenosing tumor the sarcomatous nature of which was revealed by biopsy Diagnosis of perforation was made in all cases before operation but in none was it recognized as cancerous Aird has reported 79 cases from the literature At Baron's hospital there were *400 ulcer perforations in 12 years but only 3 were cancerous* Males predominated 75 per cent of the 79 patients mentioned in the literature and all 3 of the author's patients were men Operation is indicated to save the patient but surgical mortality is approximately 68 per cent The cancers are usually prepyloric Intervention should be limited in most cases to simple closure of the perforation sometimes combined with gastroenterostomy Roentgen examination is valuable in diagnosis because spontaneous pneumoperitoneum is often pathognomonic of perforation

[Acute perforation or gross hemorrhage especially in the early recognizable stages of gastric cancer is admittedly infrequent This is particularly true in the polypoid or fungating type of cancer that grows into the lumen of the organ rather than outwardly

(7) Rev clín españ. 5 96 Apr 30 1942

toward the serosa. But why a carcinomatous ulcer morphologically indistinguishable from a benign one and now constituting 13 per cent of our resected cases does not have the same perforating potentialities is not clear As a matter of fact I think it has especially in the presence of an adequate acidity but its malignant nature is not recognized at the time —Ed]

Incidence of Malignancy in Prepyloric Ulcers B R Kirklin and William C MacCarty Jr [8] state that the prevalent assumption that prepyloric ulcers are more likely to be malignant than ulcers elsewhere in the stomach has been challenged in recent years Records of ulcerous prepyloric lesions observed roentgenographically and operated on at the Mayo Clinic from 1937 to 1941 were reviewed subject to the commonly accepted concepts of simple ulcer malignant ulcer and ulcerating carcinoma All ulcerating carcinomas that had been diagnosed roentgenographically were excluded After other exclusions made necessary by the roentgen approach there remained 61 ulcerating carcinomas and 71 ulcers of which 63 were benign and 8 malignant These figures are compatible though not identical with the generally accepted estimate that 10 12 per cent of all gastric ulcers including many that appear roentgenographically and macroscopically to be benign prove to be malignant This study thus supports the newer view that prepyloric ulcers are not more often carcinomatous than gastric ulcers in other situations

The highly diverse estimates as to incidence of malignancy in prepyloric ulcers evidently result from varying definitions and applications of the term ulcer According to the classification used in the present study the term ulcer with or without the qualifying adjective benign or simple implies a nonmalignant peptic ulcer the crater of which is sculptured in the gastric wall with a diameter seldom exceeding 2 5 cm and without any tumefaction of its borders except in the rather uncommon instances of callous ulcer The designation malignant ulcer is restricted to a lesion that has the morphologic characteristics of benign ulcer but on microscopic exam

(8) J A M A 1 0 733 735 No 7 1942

ination is found to be carcinomatous The term ulcerating carcinoma speaks for itself it is helpful to confine it to ulcerating carcinomatous tumors in which both ulceration and tumefaction are demonstrable either macroscopically or roentgenographically, thus distinguishing these malignant tumors from malignant ulcers

Of much greater importance than the exact incidence of malignancy in prepyloric ulcers as strictly defined is the fact that many lesions in this part of the stomach are ulcerous and malignant

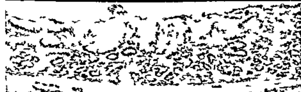
Stomach in Pernicious Anemia In view of recent evidence suggesting contrary to previous reports, *that* in man the site of production of intrinsic factor' is the fundus and body of the stomach, it is pertinent to reconsider the gastric changes in patients with pernicious anemia Findings in six cases of pernicious anemia in which autopsy was done and the stomach *studied anatomically are reviewed by Alvin J Cox*[9] (Stanford Univ) In two of the cases continuous successful liver therapy had been given for many years

Dissection was accomplished easily There was no unusual adhesion of the mucosa to the remainder of the stomach wall in any case An outstanding characteristic *was the marked alteration in the mucosa of the fundus* and body (referred to as the fundic zone) in contrast to the relative freedom from abnormalities in the pyloric region There were slight alterations in the pyloric zone in several instances two showed unusual numbers of cells *in the interstitial tissue in three there were scattered Russell bodies and in two there were single small* protruding mucosal nodules in this region In two cases the pyloric zone was considered normal throughout (Fig 96) and except for the presence of polypoid nodules, the changes in the pyloric zone in the other cases were not distinguishable from those occurring in many persons of *comparable ages*

In the *fundic zone* the changes were extensive and severe The mucosa was only about half the thickness of

(9) Am J Path 19 491 501 May 1943







F g 94 (top).—C se 5 Stom h pe ed l g gr te curv t sh ws v ry th f d with ly v bl bm sal sel t ast g with pylori zo of n rm l th k pt f gl m ll polyp d nodul

F g 9 (ent)—Cas 4 Sect f f l p rt f g t m os b or m l h t tu w th irregula ly rr g d, sm ll tort us gl ds e ti ly d id f pa t l and h f ll Hem t yl -eo ed d f m × 92

F g 96 (bottom)—S me se p er d g Norm l pyl p rt f g tri Hem to yli -eo i d d f om × 9

that in the pyloric zone Even in the gross specimens this difference was apparent, producing a fairly sharp distinction between the zones (Fig 94) The abnormal thinness was not due to postmortem changes but was a manifestation of a completely abnormal type of mucosa in the fundic area, in which the normal specific cell types (parietal and chief cells) were absent The mucosal glands (Fig 95) were shorter, less numerous and more tortuous than those of the normal fundic region The arrangement was irregular and some glands were separated from one another by loose connective tissue The deeper lining cells were cuboidal and fairly uniform but were faintly stained and had no distinctive morphologic characteristics Some glands had formed small cysts but these were not numerous in any case Scattered through the abnormal mucosa in all stomachs were easily demonstrable and sometimes numerous, coarse, deeply stained glands showing structural features characteristic of mucosal glands in the small intestine Some of these atypical structures occurred singly and some were in groups which had completely replaced other glands These glands of intestinal type contained goblet cells and Paneth cells with prominent eosinophilic cytoplasmic granules were usually prominent in the basal portions In one of the cases in which treatment had been successful for many years similar granules were also present in the cells of small glands which were tortuous and occurred in well defined but not encapsulated clusters However this appearance was not evident in the second case in which prolonged treatment had been given In four of the stomachs there were considerable numbers of interstitial cells resembling lymphocytes and plasma cells among the abnormal mucosal glands but in two cases these were not numerous Similarly although Russell bodies were abundant in the fundic zone in three cases they were practically absent in the other three None of the findings varied in consistent relationship to the known duration of the disease or of the therapy

The loss of specific cell types in the mucosa of the fundic zone was complete in all except one case in which a few small groups of atypical glands containing a few cells resembling parietal cells were present in the sections taken from the upper portion of the lesser curvature No chief cells were seen and no parietal cells were found in any other portion of this stomach

Examination of the stomach in one case of nontropical sprue disclosed none of the changes which characterized the stomachs in the cases of pernicious anemia This is in accord with reports of demonstration of normal amounts of free acid in the gastric juice from patients with sprue but does not support the view that some degree of gastritis is present in this disease

It is suggested that the gastric lesions in pernicious anemia may represent a specific change perhaps the result of massive destruction of the highly differentiated parietal and chief cells

Association of Pernicious Anemia and Carcinoma of the Stomach is discussed by Paul C Doehring and George B Eusterman[1] From 1935 to 1939 1 014 patients with pernicious anemia were seen at the Mayo Clinic Seventeen had carcinoma of the stomach also—an incidence of about 1 7 per cent which seems slightly greater than the calculated incidence of gastric carcinoma among the general adult population The findings in these cases are given in the table The carcinomas were similar in situation and grade of malignancy to carcinomas of the stomach not complicated by pernicious anemia The average age at which onset of symptoms of pernicious anemia occurred was 54 5 years while that at which symptoms of gastric carcinoma appeared was 63 2 years Although present evidence is insufficient to prove a direct relation between the two diseases there are grounds for suspecting that persons with pernicious anemia are slightly more likely to have gastric carcinoma than normal persons

(1) Ar h S g 45 554 563 Oct be 1942

DATA ON 17 CASES OF PERNICIOUS ANEMIA ASSOCIATED WITH GASTRIC CARCINOMA

Sex	Pernicious Anemia: Onset *	Pernicious Anemia: Gastric $\frac{1}{2}$ Hay†	Interval Between Diseases, Yr	Carcinoma of Stomach: Onset *	Carcinoma of Stomach: Site	Carcinoma of Stomach: Treatment	Carcinoma of Stomach: Grade	Result
M	5[illegible]	N	0	[illegible]	Middle 1/3	Partial gastrectomy	3	Died aged 6
F	57		0	[illegible]	Lower 1/3	None		Refused operation
F	5[illegible]		2	[illegible]4	Lower 1/3	Local resection	2	Died aged 57
M	[illegible]4	N	3	[illegible]	Upper 1/2	None		Carcinoma inoperable
M	6	N	[illegible]	[illegible]0	Upper [illegible]3	Exploratory laparotomy		Died aged [illegible]0
M	5[illegible]	N	6	63	Middle 1/3	Partial gastrectomy	4	Died aged 64
F	[illegible]2	N	8	60	Lower 1/3	Partial gastrectomy	2	Well aged 63 (April 1940)
M	[illegible]4	N	9	63	Middle 1/3	Exploratory laparotomy	4	Died aged 63
M	4[illegible]	N	10	[illegible]5	Lower 1/2	None	2	Carcinoma discovered at autopsy
M	[illegible]0	N	1[illegible]	6[illegible]	Lower 1/3	Exploratory laparotomy	3	
F	46		12	58	Lower 1/3	Exploratory laparotomy		Died aged 59
M	45		12	[illegible]7	Lower 1/3	Partial gastrectomy	3	Well aged [illegible]8 (Oct 1940)
M	[illegible]5		1[illegible]	67	Lower 1/3	Partial gastrectomy	1	Well aged 68 (Oct 1940)
F	[illegible]	N	13	[illegible]5	Middle 1/3	Local resection	2	Died aged 8
M	54		14	68	Entire	Exploratory laparotomy		
M	[illegible]8		15	73	Upper 1/3	None		Carcinoma inoperable died aged 74
M	42		15	57	Entire	None		Carcinoma inoperable

* As nearly as could b j dg d f m signs and symptoms

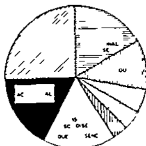
† At n a the time the diagnos s of p rnicious an m a was made V in d tea normal.

Gastro Intestinal Disease among Industrial Workers

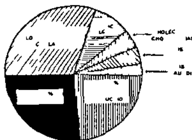
Lemuel C McGee (Wilmington Del) and J D Creger

( ) J A M A 1 0 1367 1369 Dec 6 194

(Pulaski Va) report absentee figures representing the predominantly male personnel of several plants varying in size from less than 100 to more than 4 000 employes Occupations varied from office work to outdoor construction labor This group lost 40 943 days of their expected working hours from all causes an average of 4 1 days per employe per year There were 34 018 days lost because of sickness and 6 925 days lost because of accidental injury The relative importance of the broad causes of absenteeism is shown for severity in Figure 97 Of the total 7 605 days lost because of gastro intestinal disease 79 8 per cent of the time lost was due to acute digestive upsets dysfunction of the colon acute appendicitis hernia and intestinal obstruction (Fig 98) The designation gastro intestinal upset includes instances of irritable colon the nausea of postalcoholic malaise and abdominal discomfort of uncertain origin



F g 97 —Cause of 40 94 d ys lost tim (ty)



F g 98 —C u of 7 605 d ys lost t m fr m disease of dig ti yst m (seve ity)

These experiences lead the authors to question whether all opportunities to practice preventive medicine are employed The workman needs to replace erroneous ideas by factual and correct concepts for the care of his health It is most likely that workmen will welcome and respond to the precepts of physicians who take time to explain

useful health facts The personnel of industry welcomes knowledge *concerning the functions of the* human body and the causative factors of ill health

Digestive Disease and Military Service John L Kantor[3] *states that digestive diseases play a prominent* role in military medicine both in peace and in war The most important of these in the present war are the intestinal fluxes peptic ulcer digestive neuroses and possibly *gastritis Peptic ulcer ranks high as a* cause of disability for military service It is increasingly common in both the civilian and the military population and leads all other digestive diseases as a cause for discharge from the Regular Army A critical survey of the present recruiting policies indicates that they are probably effective in excluding ulcer bearing candidates from the United States Army *In addition to exclusion of* dyspeptic persons from the Army by careful recruiting prophy*laxis of digestive disease can be accomplished* by immunization against specific intestinal infections supervision of food supplies and enforcement of general sanitary measures Excellent professional care of soldiers with digestive disease is now made possible by proper utilization of specialists and by establishment in larger military hospitals of well equipped and well organized sections of gastro enterology

Opportunities for research on the relation of digestive *disease to military service should be cultivated* Among the problems for investigation are utilization of ulcer predisposed patients *for limited service status of chronic* gastritis as a service-connected disability and value of chemotherapy in early treatment of bacillary dysentery Comparison of records from World War I with those of the Veterans Administration suggests that of every nine soldiers who exhibit digestive disease in active service three or four are likely to continue to have permanent digestive disability Data now being compiled by the Selective Service System the Medical Department *of the Army* and the Veterans Administration together

(3) J A M A 1 0 4 60 Sept 6 194

with the records of World War I should constitute excellent source material for future studies on the relation between digestive disease and military service

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DISEASES OF THE BILIARY TRACT AND PANCREATIC SYSTEM

Effect of Sulfanilamide on Experimentally Damaged Liver is reported by Thomas E Machella and George M Higgins[4] (Mayo Clinic) Sulfanilamide (1 Gm per Kg body weight) was given in suspension by stomach tube to adult male albino rats (1) in which hepatitis had been induced by inhalation of carbon tetrachloride (2) in which hepatitis was being induced by carbon tetrachloride (3) to which alcohol was being given and (4) in which obstructive jaundice had been induced by common duct ligation Suspension was in tap water except in the experiments with alcohol when it was in 20 per cent alcohol. The rats were fed a standard commercial stock diet and had access to fresh water

Administration of sulfanilamide to the rats in which hepatitis was being induced by carbon tetrachloride did not increase liver damage On the contrary necropsy revealed less damage Administration of sulfanilamide after induction of hepatitis did not impede the liver regeneration occurring after use of carbon tetrachloride had been discontinued Simultaneous administration of alcohol and sulfanilamide did not damage the hepatic cells although droplets of fat were found in the hepatic cells of the animals which received only alcohol The animals with biliary obstruction showed no liver damage traceable to sulfanilamide

These data are in accord with clinical data which show that sulfanilamide or allied compounds do not increase hepatic dysfunction in patients to whom they are administered.

Influence of Vitamin B Deficiency on Experimental Liver Necrosis was investigated by Ralph M Calder[5]

(4) Am J M Sc. 204 194 01 A gust 194
(5) P th & B ct 54 355 368 July 1942

(University College Hosp Med. School London) with the idea that study of some of the factors which influence liver necrosis might throw some light on etiology of human cirrhosis Experiments revealed that dietary balance of choline and a thermolabile factor in the B complex has an influence on the degree of liver damage in rats following subcutaneous injection of chloroform The thermolabile factor is not vitamin B_1 It is present in yeast is insoluble in alcohol and is destroyed by autoclaving It may therefore be identical with factor W, but for convenience it has been termed factor N Vitamin B_1 deficiency has no influence on the degree of liver damage caused by chloroform Deficiency of factor N with adequate choline or the converse will increase liver damage over that in animals in which both factors are adequate or both are deficient These effects cannot be explained on the basis of alterations in liver fat or liver glycogen

Infective Hepatitis J C Ford[6] reports an outbreak of 300 cases of infective hepatitis in an outer London borough One case terminated fatally necropsy disclosed acute yellow atrophy of the liver The source of infection is unknown Most patients reported close contact with other persons who either had the disease or had just recovered

Most patients had well marked prodromal symptoms such as mental depression irritability or drowsiness with loss of appetite and constipation headache and pain in the right epigastrium Many complained of shivering attacks and a few of muscular tenderness or photophobia Eight patients presented coryza at the onset After three or four days nausea and vomiting would appear together with a temperature rise to about 101 F Bile appeared in the urine on the fifth or sixth day followed in 24 to 48 hours by jaundice Jaundice was first evident in the conjunctivas and spread to the face neck abdomen and entire body With onset of jaundice there was in most cases an improvement in the general condition The

(6) L cet 1 6 6 8 May 9 1943

mental depression and drowsiness and usually the vomiting disappeared and within a few days the appetite returned The stools were acholic Some patients presented oliguria but with appearance of the biluria there was a return to normal volume Moderate hepatomegaly was found in all patients examined but the spleen was not palpated in any of these Jaundice would persist for one to three weeks in one patient it was evident for eight weeks

In mild cases after the initial symptoms of headache nausea and epigastric pain transient biluria occurred but this was not followed by jaundice even of the conjunctivas It must be assumed however that these patients are as infectious as those more severely affected

A droplet spread of infection has been suggested but not proved During an epidemic children who vomit in school should be excluded for seven days

[The old term catarrhal jaundice has been replaced by the term infective or epidemic hepatitis particularly by European authors. In the light of present knowledge the latter is undoubtedly the more appropriate designation Briefly the cause or causes of the disease are not known and there is no specific diagnostic test A virus is under suspicion In doubtful cases of fever with jaundice leptospirosis (Weil s disease) or even yellow fever might be suspected Most of the cases I see are of sporadic rather than of epidemic nature —Ed]

Functional Value of the Liver in Heart Disease Ignacio Chavez B Sepulveda and A Ortega I[7] (Mexico City) report that during heart failure liver functions are profoundly disturbed Blood bilirubin determinations and determinations of bromsulfalein and urobilinogen of the urine are positive as a rule are perceptibly parallel to each other and usually keep a definite relationship with the degree of heart failure Similarly tests which proved to be abnormal during heart failure reverted to normal when the latter disappeared When there is only improvement of the circulatory condition results of the liver tests parallel such improvement

In cases of heart failure functional hepatic disturbance does not usually keep a definite relationship with

(7) J A M A 121 1276 1 8 Ap 17 1943

the cause of the heart condition itself However according to the employed tests the most accentuated hepatic disturbances are usually found in the group with rheumatic heart disease

Because of circulatory disturbances the galactose clearance test is of no value as a test of hepatic function in heart failure

Cirrhosis of the Liver is discussed by Reginald Miller[8] (St Mary s Hosp London) Cirrhosis of the liver is a pathologic term denoting development of new fibrous tissue in the liver irrespective of its cause or type It is also commonly used as a clinical term signifying a particular form of hepatic fibrosis which leads to a clinical syndrome ultimately including hematemesis and ascites In this sense then use of the term is restricted to the multilobular type of hepatic fibrosis which is usually associated with alcoholism Also requiring mention is the disease splenic anemia in which in its later stages multilobular cirrhosis of the liver (Banti s syndrome) with ascites tends to develop

In multilobular cirrhosis (portal cirrhosis hobnail liver) combined with degeneration of the hepatic cells fibrosis spreads from the portal spaces enclosing groups of lobules of liver substance The liver is commonly enlarged from congestion hyperplasia and fatty degeneration in the later stages it tends to shrink from the excess of fibrosis and may be much smaller than normal The liver is hard to the touch and its surface is studded with small projections *The fibrosis leads to obstruction* of the intrahepatic branches of the portal vein This in turn results in dilatation in the collateral circulation between the portal and general venous systems

Pericellular cirrhosis is peculiar to congenital syphilis The liver is enlarged and hard and the spleen may be enlarged Other evidence of infection is usually present and the blood reactions are positive

Perilobular cirrhosis (biliary cirrhosis) results from the hepatitis set up by infection and obstruction of the

(8) Pr ctto r 150 71 76 M y 1943

bile ducts Jaundice is constantly present in these cases

Hanot s biliary cirrhosis seems now to have so completely disappeared that there is a doubt whether it ever existed as a real entity or was a mixture of ordinary biliary cirrhosis splenic anemia and acholuric jaundice It was formerly described as occurring chiefly in children being sometimes familial and showing enlargement of the liver and spleen with jaundice and clubbing of the fingers

It will be agreed that for many of these conditions a clinical diagnosis of cirrhosis of the liver would be inadequate

Splenic anemia is a disease of unknown origin and is most commonly seen in young adults Its course which lasts 5 12 years includes three stages (1) symptomless splenic enlargement (2) symptoms of discomfort in the splenic region hypochromic anemia with leukopenia (2 000 5 000) and hematemesis (3) symptoms of hepatic cirrhosis including ascites and jaundice Some however hold that the hepatic cirrhosis is not necessarily secondary to toxic absorption from the diseased spleen but is an independent and possibly primary manifestation of the disease This has an important bearing on the theory of splenectomy in treatment of the disease Hematemesis may occur early or late in splenic anemia and tends to be copious and repeated It is commonly derived from the enlarged veins of the gastrosplenic omentum and more rarely from the dilated veins in the lower part of the esophagus as in alcoholic cirrhosis If the term Banti s syndrome is to be used it should be restricted to those cases in which there is clinical evidence of hepatic cirrhosis Ordinarily splenic anemia presents itself as splenomegaly and has to be distinguished from myelogenous leukemia acholuric jaundice and other conditions presenting splenomegaly

Treatment consists of splenectomy unless the patient is already seriously ill from advanced hepatic cirrhosis Two arguments are advanced against splenectomy (1) It is not certain that the hepatic disease is secondary to

and dependent on, the disease of the spleen and (2) some authorities state that death will ultimately occur from hepatic cirrhosis even though splenectomy has been performed early Miller however believes that splenectomy may often cause distinct improvement and that the patient's blood may be kept at a satisfactory level after operation by the same iron therapy which had failed to effect improvement before operation

In splenic anemia splenectomy is always a serious and sometimes a most difficult operation Formidable adhesions may exist between the spleen and perijacent organs Postoperative thromboses constitute a further danger, this is due to increase in blood platelets for a short period after operation To obviate this danger use of heparin has been suggested

Treatment of Acute Cholecystitis is outlined by Robert Zollinger and Elliott C Cutler[9] (Peter Bent Brigham Hosp) In their program the patient is hospitalized as soon as diagnosis is made This permits institution of treatment which will prepare the patient for operation at an ideal time The extent and severity of the inflammatory process are estimated by physical examination and an evaluation of the general condition Accepted conservative measures are then instituted (1) relief of pain by morphine (2) semisitting position with heat to the abdomen (3) administration of fluids intravenously or subcutaneously to hydrate the patient properly and (4) constant gastric suction if the patient is vomiting or is distended Routine laboratory studies are made

Although many patients with acute cholecystitis respond promptly to treatment the possible concomitant complications must not be disregarded Even in mild cases the signs symptoms and laboratory data should be evaluated at frequent intervals In severe cases, this should be continued throughout the night

To ascertain subsequent treatment for each patient and to determine safely the optimal time for early or late

(9) J A M A 1 1 481-485 Feb 13 1943

surgery, three major clinical groups are distinguished The first comprises the majority of patients and in these signs and symptoms subside after adequate treatment with rest and fluids and relief of pain These patients are sometimes well prepared for surgery within five or six days However many clinical variations of this group are encountered For example some patients present minimal signs and symptoms of acute cholecystitis perhaps because the attacks have been mild or because the physician was not called until the acute episode had subsided Such patients are best hospitalized even during a first attack They usually respond promptly to conservative measures and can be operated on without undue risk within 18 hours of admission Other patients with more pronounced symptoms respond promptly to conservative treatment within 48 hours with return to normal of temperature leukocyte count and physical findings If operation is not conducted when proper hydration is obtained a few of these patients will experience exacerbation after 48 hours It is impossible to predict the course of their disease when treated conservatively hence early hospitalization and surgery are urged Many other patients show slow but progressive improvement with subsidence of acute manifestations after three days Although it is desirable to operate early in these cases operation may be delayed when progress is satisfactory

The second group includes patients whose temperature leukocyte count and physical findings remain practically constant with no response to initial treatment Operation should not be delayed in this group and should be performed within 36 to 48 hours after the fluid balance has been adjusted

The third clinical group is made up of the small number of patients whose signs and symptoms show rapid progress They are acutely ill and usually require simple gallbladder drainage as soon as possible

In any instance emergency surgery is rarely required The report a mortality rate of 2 6 per cent in the

surgical treatment of 146 patients with acute cholecys titis The incidence of associated common duct stones was 14 9 per cent The low mortality is ascribed to indi vidual treatment of each case

[In view of the emergency nature of some cases of acute cho lecystitis with the impending threat of gangrene, perforation and rapidly fatal peritonitis the authors conservative attitude is commendable It is a fitting answer to the arguments of that clamorous though small group of surgeons who would operate at once in every case Conservatism in acute pancreatitis is even more justifiable However the acutely inflamed appendix is another story —Ed]

Biliary Dyskinesia According to Howard K Gray and Wendell S Sharpe[1] (Mayo Clinic), the two most probable causes of biliary dyskinesia are (1) erroneous diagnosis of cholecystitis and ill advised removal of the gallbladder with persistence of some functional disorder of the choledochus sphincter and (2) residual inflamma tory disease of the liver pancreas or ductile system The possibility that some inflammatory or mechanical lesion of the cystic duct may cause typical symptoms of cho lecystic disease suggests that a similar lesion in a rem nant of cystic duct may be the obscure cause of persistent pain after cholecystectomy In many cases removal of this remnant has been coincident with choledochostomy and choledocholithotomy If the original operation was performed on the basis of adequate historical or roent genographic indications or both about 70 per cent of the patients have been found to obtain relief of persistent symptoms by the second operation in which the cystic duct with or without stones was removed

In the authors series of 44 cases all specimens of cys tic duct removed showed evidence of disease in 35 cases there was evidence of recent inflammation

In 26 cases of biliary dyskinesia in which at the second operation only an enlarged inflamed remnant of cystic duct was incriminated and removed approximately 65 per cent of the patients were relieved of their symptoms provided the first operation was well advised and neces sary If the first operation was performed on the basis

(1) A ch S g 46 564 571 Ap il 1943

of inadequate indications 100 per cent failure resulted from the secondary operation in which only drainage of the common bile duct or removal of a remnant of cystic duct could be accomplished

Too great stress cannot be placed on the importance of operating only in those cases with definite and conclusive clinical or roentgenographic evidence of disease of the biliary tract At operation meticulous care must be exercised to avoid damage to the common bile duct but at the same time all but a small remnant of the cystic duct should be resected In those cases in which the patient unfortunately experiences persistence or recurrence of pain after cholecystectomy and in which reoperation is deemed necessary diligent search should be made for a remnant of the hepatic duct whether or not calculi are suspected in the common bile duct

Jaundice in the Tropics Philip Manson Bahr[2] (Hosp for Tropical Diseases London) reviews the various tropical *diseases in which jaundice may occur*

Jaundice is a frequent concomitant of only one form of malaria the subtertian or malignant in which hemolysis takes place on such a scale as to produce bilirubinemia and tinging of the scleras and skin There is polycholia too which characterizes that severe clinical type of malaria known on the west coast of Africa as bilious remittent in which with other evidences of toxemia persistent and distressing bilious vomiting occurs The skin assumes a yellow ocher tint liver and spleen are both enlarged and sometimes tender and painful. An indirect positive van den Bergh reaction is found in the serum With each severe crisis in subtertian malaria a certain degree of hemolysis is produced so that a transient hemoglobinemia occurs

Recurrent urobilinuria constitutes a valuable clinical sign and this test may often be used in cases in which the subtertian parasites are either scanty or cannot be detected in the peripheral blood

Deep jaundice of the toxic type is less frequent but

( ) P rtt 150 65 70 M 1943

may occur in overwhelming falciparum infections It is believed that in such instances focal necroses of the liver have taken place Bilirubin is present in the urine and bilious vomiting occurs The spleen is enlarged and tender and prognosis is grave

The mechanism of these processes is regulated by biochemical changes Hemoglobin from the disintegrated corpuscles is broken down into hemosiderin which is deposited in the liver spleen and kidneys The hemobilirubin which circulates in the blood causes hemolytic jaundice The excess is converted in cholebilirubin which *results in bilious vomiting and urobilinuria*

The obstructive form of jaundice may also occur as a sequel to subtertian malaria It is often accompanied by gallstone colic and is due to formation of pigmented calculi the direct result of excessive bile secretion

Jaundice has been reported to occur in acute cases of kala azar The pathology is not clear but in chronic cases fine intracellular fibrosis of the liver has been noted this results in ascites and a clinical picture of hepatic cirrhosis making differential diagnosis difficult Jaundice of the obstructive type has been noted The invari*ably enlarged spleen and the associated hyperglobulin*emia assist differential diagnosis

Both the louse borne and the tick borne varieties of relapsing fever present examples of hemolytic icterus In severe cases this feature develops in the precritical period and coincides with spirochetolysis in the peripheral blood This hemolytic icterus is comparable to that in subtertian malaria The serum gives an indirect positive van den Bergh reaction and there is increased urobilinuria

In yellow fever there occurs the most intense icterus produced by a filtrable virus Jaundice is noted on the third day staining the skin and scleras a golden yellow Sometimes the color is more saffron or it may be mahogany brown In milder infections or in the partially immune the fever may be slight and icterus absent The hemorrhagic tendency which chara

ease is shown by the deep blue stains produced by subcutaneous effusions of blood In this disease icterus is probably partly hemolytic and partly toxic due to diffuse liver necrosis

Other tropical diseases which may be associated with jaundice due to liver infection include bilharziasis (schistosomiasis) and clonorchiasis due respectively to blood flukes and liver trematodes Jaundice may be sometimes found as a sequel to infections with the typhus group of organisms and it is also found in the convalescent stages of cholera

Manson s Schistosomiasis is discussed by Enrique Koppisch[3] (San Juan Puerto Rico) The great endemic foci are Africa northern South America and the Caribbean region The disease is acquired through exposure to cercariae usually while bathing in infested streams or while working in irrigation canals but infection can also take place through the buccal mucosa while drinking infested water The cercariae penetrate the epithelium entering either lymphatics or veins and are carried to the lungs After entering the host the organisms are known as metacercariae The course followed by the metacercariae seemingly is strictly intravascular Those which survive the pulmonary circulation reach the left side of the heart from which they gain access to all organs and tissues Some obstruct capillaries giving rise to petechial hemorrhages and many are lost during their *wandering Finally those which reach organs and* tissues whose venous drainage is by way of the portal vein seem to be the only ones which become established in the mammalian host By passing from the arterial to the venous side in organs like the liver spleen pancreas stomach and intestine they reach intrahepatic portal branches where they attain maturity

Mature males and females wander against the blood current and copulate in the larger venous tributaries of the portal vein showing strong preference for the lower colonic and rectal branches Ova are deposited by

(3) J A M A 121 936 942 Ma 20 1943

the females in the visceral venules The ova may remain against the endothelium of the venule, or they may be transported by the blood to organs such as the liver

It is probable that in man most of the damage is accomplished by the ova The tissue reaction evoked by their presence consists of pseudotubercle formation, the initial and final stages of which are shown in Figures 99 101 The presence of ova leads to progressive fibrosis of the hepatic portal spaces and submucosa of the colon



F g 99 —Sect on of hum n l e infilt t n f polymo ph ucl leukocyte about o um × 405 (P to R c J P b He lth & Tr p M d 16 395 M ch 1941)

with the ultimate development if sufficient ova continue to be deposited over several years of portal cirrhosis and splenomegaly Associated with cirrhosis is portal obstruction resulting in development of collateral circulation this may include esophageal varices from which fatal hemorrhage may occur Splenomegaly develops not so much from deposition of ova in the spleen as from portal obstruction and the general reticulo endothelial response to the infection

The early period of infection in man is usually asymptomatic exception being made of itching for a few hours over the parts exposed to the infested water The intermediate stage ensues with onset of oviposition about 40 days after exposure Symptoms at

abrupt onset with fever with or without chills having a remittent or intermittent course and reaching 102 104 F daily This may endure for two or three weeks or longer if untreated Also during this period there occur

F g 100 (t p) —S t f h m l p eudot b l lm t mpl tely fib ed gg h ll n t × 90

F g 101 (bott m) —S t f h m n l fib d l m k g fi l t g h l g f p d tub l × 90 (P rt R J P b Health & T p Med 16 39 M h 1941)

generalized or localized abdominal discomfort nausea vomiting abdominal distention dysenteric manifestations urticaria and cough Physical examination may disclose patchy areas suggestive of bronchopneumonia and enlargement of the spleen and liver There may be ... eosinophilia

The gravity of the symptoms and the outcome of the disease depend on the extent of the infection and on whether oviposition can be stopped through destruction of the adult worms before the hepatic fibrosis becomes *a true cirrhosis It is usually 10 12 years before frank* cirrhosis develops

In the late stage the clinical picture is dominated by manifestations of cirrhosis with splenomegaly, ascites anemia and cachexia Diagnosis at this stage depends on the clinical history, presence of eosinophilia, repeated search for ova in the stools utilizing concentration *methods, and exploratory laparotomy with liver biopsy* Fairley s complement fixation and cutaneous tests as well as Taliaferro s precipitin test, hold great promise as aids in diagnosis

[Intra abdominal disorders and hepatosplenic enlargement take on added clinical significance when Johnny comes marching home from tropical lands To be borne in mind and definitely excluded are chronic malaria schistosomiasis kala azar and amebiasis —Ed]

What Conclusions May be Drawn from Bilharzia Cirrhosis as Regards the Problem of Hepatic Cirrhosis? Rudolf Jaffe[4] (Caracas Venezuela) states that bilharzia cirrhosis caused by Schistosomum mansoni being *a dis* ease of known etiology in which the various changes in the liver are but different stages of the same process affords an opportunity for certain conclusions with reference to hepatic cirrhosis

Hepatic cirrhosis is not a disease limited to the liver but rather a systemic disease in which the changes in *the liver are merely manifestations* in a particular organ. Despite the generalization of the disease the changes in the liver may represent the only demonstrable pathologic organ alterations in some cases while in others the spleen and other organs may *be involved* The essential pathologic feature in hepatic cirrhosis is parenchymal damage Primary damage to other tissue components has not been demonstrated It is not likely that such damage exists all changes in the other struc

(4) S hw m d Web sch 72 1149 1154 Oc

tures of the liver such as the stellate cells the reticular fibers and connective tissue cells are secondary to parenchymal alterations On the degree and distribution of these parenchymal changes depend all other pathologic changes and as in bilharzia varying pictures of liver cirrhosis may result from the same cause It is irrelevant whether the disease is designated as chronic inflammatory or as a transformation process The essential thing is the knowledge that parenchymal injury is the primary feature and all other processes are regenerative reparatory and irritative productive secondary to this parenchymal damage The classification of liver cirrhosis according to the anatomic aspect is illogical since so many different pictures may be produced by the same cause It is therefore a matter of opinion whether cirrhosis of the liver which is a true entity should be subdivided arbitrarily into several different groups Jaundice should be considered as a concomitant symptom due to the same parenchymal damage mechanical factors playing little if any role in its etiology

Effect of Pancreatectomy on Fat Absorption from the Intestines Cornelius Vermeulen Frederick M Owens Jr and Lester R Dragstedt (Univ of Chicago) report that the temporary hyperlipemia which may be produced in normal dogs by oral administration of neutral fat or fatty acid is abolished by removal of the pancreas and is not restored by administration of active pancreatic juice or raw pancreas Pancreatectomy produces a varying degree of impairment in absorption of neutral fat but some animals may still absorb 75 per cent or more of the fat in the diet It also produces a definite impairment in absorption of fatty acid though not so great as in the case of neutral fat

External Pancreatic Fistula Mandred W Comfort Arnold E Osterberg and James T Priestley[6] (Mayo Clinic) report a case with physiologic observations

a J Phy l 138 792 796 Ap ll, 1943
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The fasting secretion of pancreatic juice through the external fistula, when the gastric juice was excluded from the duodenal cavity was low in volume and in total bicarbonate and enzyme content The fasting secretion of pancreatic juice through the external fistula when the gastric juice was allowed to enter the duodenal cavity was variable but for the most part low in volume and bicarbonate content The secretion of pancreatic juice through the external fistula when gastric juice was excluded from the duodenum was not measurably stimulated by glucose and casein and was only slightly stimulated by olive oil introduced through the duodenal tube into the duodenum

Secretion of pancreatic juice through the external fistula was stimulated vigorously by glucose and casein administered orally The effect of glucose and casein was similar to that obtained by administration of purified secretin They effected an increase in volume and an increase in the total secretion of bicarbonate amylase and lipase just as purified secretin does The secretion of pancreatic juice through the external fistula and its content of bicarbonate and lipase was not stimulated and was probably depressed by olive oil administered orally the secretion of amylase on the contrary appeared to be mildly stimulated The type of secretory response of volume of bicarbonate and of enzymes seemed to depend first on the gastric secretory response to food and emptying time of the stomach and second, on the effect of gastric secretion on the secretin mechanism The type of secretory response did not appear to depend as much on the effect that food exerts directly on pancreatic secretion as on the effect of foods on gastric secretion Gastric contents (gastric secretion plus food) was a much more potent stimulant of pancreatic secretion than were foods alone

The secretion of pancreatic juice through the external fistula after the administration of mixed meals depended on the proportion of the different foods present in the meal Meals low in fat and high in ca -

protein stimulated a greater flow of all components of the pancreatic juice than did the meals high in fat

Ephedrine sulfate and atropine sulfate decreased the fluid volume and values for total bicarbonate and lipase but did not materially diminish the total amylase values of pancreatic juice secreted through the external fistula Secretin in the doses given appeared to be equal to or somewhat more potent than did the normal secretin mechanism stimulated by a meal in producing secretion of pancreatic juice for each unit of time Mecholyl chloride did not appreciably increase the secretion of fluid volume or bicarbonate to more than fasting values Secretin plus mecholyl chloride evoked a greater secretion of all components of external secretion than did any other stimulant used

Pancreatic Disease Joseph H Pratt[7] (Boston) believes that it is not disturbance of fat digestion and absorption that is of greatest importance in diagnosis of pancreatic insufficiency but disturbance of protein digestion After study of a series of cases he is convinced that presence of many undigested muscle fibers in the feces when the patient is on a diet rich in meat is the simplest test of greatly diminished or absent pancreatic external secretion.

Over a period of years Pratt studied the effect of excluding all pancreatic juice from the intestine in dogs His experiments proved that in every instance there was diminution in absorption of nitrogen and fat atrophy and sclerosis of the pancreas In none of the dogs did fatty degeneration of the liver occur It seems logical to conclude that the sclerotic pancreas in which both acini and islands of Langerhans are largely destroyed is able in some way to prevent development of a fatty liver That these dogs did not develop diabetes is evidence that islet cells were still present and functioning That fatty degeneration of the liver did not occur supports Dragstedt's observation that the pancreas produces another internal secretion in addition to insulin i e lipocaic

7 J A M A 120 175 18 S pt 19 1942

After a standard meal fat was well split in absence of pancreatic digestion in fact 51 6 per cent of fat in the jejunum was split apparently owing to action of the gastric lipase as 35 per cent of the fat in the stomach contents was split

That the same rapid drop in elevated diastase values occurs in acute pancreatic disease as after obstruction of the ducts or injury to pancreatic tissue was not recognized until 1930 Since then it has been found in acute

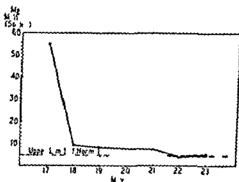


Fig 102 —Blood d ta s in acute pancreat c ne osis p d d op w thin 24 hou to almost normal

pancreatic edema and pancreatic necrosis that diastase levels in blood and urine are considerably elevated the first 24 hours after onset but may drop to normal in the following 24 hours (Fig 102) Early diagnosis of acute pancreatic edema and pancreatic necrosis is essential to avoid needless operation

Acute pancreatic edema or acute interstitial pancreatitis is the commonest form of pancreatic disease To differentiate it from biliary colic and cholecystitis routine examination of the urine for diastase should be made immediately in every case of severe acute pain in the upper part of the abdomen In two unselected cases of what appeared to be typical biliary colic Pratt made daily examination of urine for diastase activity and in both found moderately increased diastase h

urine which dropped to normal within 24 hours but rose again with return of pain (Figs 103 and 104) At operation some time later gallstones were found

The Schmidt intestinal test diet is useful in diagnosis

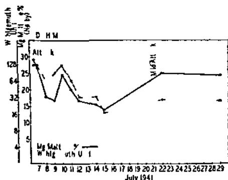


Fig 103 —U in ry d st se in acute pancreat c ed m w th cholelith a is

of obstruction of pancreatic ducts as it contains enough fat and rare meat to test functional efficiency of the

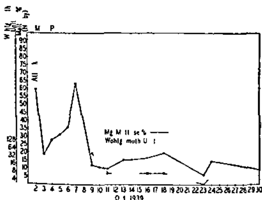


Fig 104 —U in ry d t n ut p ncr t d m w th ch l lith l

pancreas Much information may be gained from weight of the dried stools of patients on this diet In every pa

tient with steatorrhea given this diet when the stools weighed over 300 Gm obstruction of pancreatic ducts was later proved In five cases of cancer of the pancreas the greatest weight (340 463 Gm) was noted when the common as well as pancreatic duct was obstructed

Determination of nitrogen in the feces is helpful in diagnosis for the value is low in sprue and obstructive *jaundice and high in occlusion of pancreatic ducts*

Diagnosis of cancer of the pancreas is rare except in late stages Contrary to the general idea painless jaundice is not characteristic and is often a late symptom In five proved cases Pratt used the secretin test and found volume and alkalinity of pancreatic juice and concentration of enzymes greatly reduced In only one were creatorrhea and steatorrhea present Hence without the secretin test no evidence of pancreatic insufficiency *would have been discovered It is well to determine* serum lipase in all suspected cases Occasionally diastase in blood or urine is increased with cancer of the pancreas Early diagnosis permits radical operation which holds promise of prolongation of life increased comfort and possibility of cure

A New Test for Pancreatic Function has been elaborated on the dog by H L Popper and H Necheles[8] (Michael Reese Hosp Chicago) It is based on the fact that stimulation of the external secretion of the pancreas is followed by changes in the level of certain enzymes of the serum The test requires a simple injection the drawing of a few samples of venous blood and the relatively simple test for serum amylase or lipase *The drugs used are eserine acetyl beta* methylcholine hydrochloride and purified secretin preparations

Subcutaneous injection of a combination of acetyl beta methylcholine hydrochloride and eserine sulfate results in an increase of serum amylase and lipase only in the presence of a normal pancreas The amounts of these substances administered to dogs although without

(8) Gastroenterology 1 490 499 May 1943

ill effects are too large for use in man It is possible however that smaller doses of both drugs (perhaps re placing eserine by prostigmine) can be used in man with equal effects on the two blood enzymes Such a test may reveal functional insufficiency of the pancreas or the presence of more or less complete atrophy of the gland as occurs following pancreatic cirrhosis and chronic pancreatitis

Intravenous injection of relatively small amounts of secretin does not raise the level of serum lipase in the presence of a normal pancreas but does so in the pres ence of obstruction to the outflow of secretion from a more or less functioning gland In the latter case this response disappears 30-45 days after ligation of the ducts This is probably due to cessation of functional activity of the glandular tissue Fasting lipase levels usually were not increased after the tenth to fifteenth postoperative day

Purified secretin preparations can be used in man In the light of results in the dog a similar secretin test in man may be expected to reveal obstruction to the outflow of pancreatic juice such as may occur in cancer of the pancreas or of the papilla of Vater pancreatic lithiasis cysts and possibly subacute pancreatitis

[The efficacy and popularity of a clinical test are dependent in large measure on its simplic ty Such s mpl fication in labora tory procedures useful in the diagnos s of pancreatic d sease esp cially the chron c variety is timely and welcome but whether such innovation is trustworthy remains to be s en —Ed]

Postoperative Achylia Pancreatica Fat and Protein Absorption with and without Replacement Therapy Michael Lake Nelson W Cornell and Harold E Har rison[9] (Cornell Univ) report a case of successful re section of the head of the pancreas for carcinoma in a woman 2, Following operation the total absence of pancreatic enzymes was demonstrated by examination of the jejunal contents both before and after intravenous injection of secretin A marked loss of fat and nitrogen and an abnormally high excretion of calcium were found

[9] Am J M S 205 118 122 J rr 1943

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(8) Gastroenterology 1 433-438 May 1943

In several such instances there were metastases to the lymph nodes at the porta hepatis with secondary invasion of the bile ducts The fact that massive liver metastases with little remaining liver parenchyma are often unassociated with jaundice lends significance to the smaller nodules involving the intrahepatic ducts near the hilus for production of the icterus This sug-

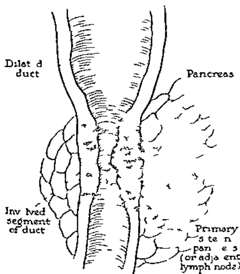


Fig 105—Mo t common m ch m of bstructi n f m p im ry te in p cr dj t lymph od This s rrb u nal progr con t ict is n in cirrh us tum of p cr m t mm n f rm

gests that in cases of massive liver metastasis also duct invasion may be a prerequisite for jaundice

The theoretical basis for cure by resection of the head of the pancreas in early cases of cancer of the pancreas despite an advanced syndrome of progressive jaundice is implied The known evolution of the syndrome of pain less progressive jaundice by stone in the duct is a further indication for early laparotomy in all cases of persistent jaundice

in the feces The fecal loss of protein and fat was markedly diminished by oral replacement therapy, but the calcium loss was not materially affected during the short period of observation. Clinical improvement and weight gain occurred The defective absorption of vitamin A in this patient was also improved during the period of pancreatic enzyme therapy The findings during a period of obstructive jaundice suggest that pancreatic enzymes are active in the absence of bile and are relatively more important than bile in the utilization of fat

[What was until recently considered a more or less useless form of replacement therapy promises to be an effective one It is essential that the pancreatic extract be a reliable product and be given in adequate dosage The efficacy of such treatment under similar circumstances has also been confirmed recently by Rekers, Pack and Rhoads *Journal of the American Medical Association* 122 1243 1245 Aug 28 1943—Ed]

Mechanism of Jaundice in Cancer of the Pancreas Naomi Kaplan and Alfred Angrist[1] (Queens Gen'l Hosp *Jamaica N Y*) *reviewed 39 cases of cancer of* the pancreas in 19 of which jaundice was present The cancer involved the head of the pancreas in 13 cases and the body or tail in 6 Carcinomatous invasion of some part of the biliary tract was present in all cases with jaundice Three separate factors are concerned in production of obstruction of the biliary tract (1) Invasion fixes the wall of the duct and permits physical compression in lieu of mere displacement by adjacent expanding tumor (2) A more common and more important mechanism is invasion of the duct wall accompanied by a scirrhous reaction with production of an annular stenosing lesion with localized segmental narrowing and obstruction of the lumen (Fig 105) (3) There may be papillary extension into the lumen in which cases sloughing may cause intermittent jaundice

An identical mechanism i e metastases to lymph nodes and then extension to biliary tract was found to account for jaundice in cases of primary cancer of the stomach and colon not associated with liver metastases

(1) Surg Gyne & Ob t 77 199 204 Au— + 1943

tion of alcohol either prior to or during treatment under which circumstances carbon tetrachloride is extremely toxic The second is severe ascariasis Carbon tetrachloride stimulates these parasites to abnormal activity resulting in the formation of solid plugs of their bodies which obstruct the intestine or in their migration anteriorly into the common bile or pancreatic ducts or the pharynx whence they may be extruded through the mouth or nose Examination for ascarides should therefore be conducted and should they be present their removal with either chenopodium or hexylresorcinol should be accomplished before carbon tetrachloride is administered

Compound anthelmintics such as mixtures of carbon tetrachloride and oil of chenopodium are highly effective for expulsion of both hookworms and round worms but it must be remembered contain elements of danger from two sources rather than only one

Closely related to and less toxic than carbon tetrachloride is tetrachlorethylene Used in the same dosage it is less effective than carbon tetrachloride but two treatments with tetrachlorethylene are about equivalent to and much safer than a single dose of carbon tetrachloride Despite its lower efficiency it is preferred because of its greater safety There are virtually no contraindications to its use except alcoholism and ascariasis

Hexylresorcinol is of incidental hookworm removal value In 1 Gm doses for adults it removes practically all round worms and about 70 per cent of the hookworms though only a comparatively small percentage of patients are rendered hookworm free with a single dose If the pills are swallowed (not chewed) there are no known contraindications and the drug can be given repeatedly even to small children aged persons and debilitated individuals It is therefore an ideal drug for pre hookworm treatment when ascariasis exists

Iron must be used as an adjuvant in treatment of ankylostomiasis both before and after anthelmintic measures if a severe anemia is present

Intrinsic Diseases of Liver Simulating Acute Cholecystitis Knowles B Lawrence (M C, A U S) and Howard M Clute[2] (Boston Univ) have found that certain *intrinsic diseases of the liver may simulate acute cholecystitis* so closely that clinical differentiation is difficult if not impossible Four illustrative cases are presented Acute hepatic disease may simulate acute cholecystitis as to sudden onset low fever elevated white *cell count and tender mass in the right upper quadrant* History of exposure to a *hepatotoxic drug should suggest* the possibility of acute yellow atrophy The clinical picture of acute *cholecystitis* may also be simulated by primary or metastatic cancer of the liver particularly *when secondary hemorrhage* or necrosis has occurred A history of *previous malignancy should arouse suspicion* of this

DISEASES OF THE INTESTINAL TRACT

Modern **Views on the** ***Treatment*** **and** ***Prevention*** **of Hookworm Disease** are discussed by Justin Andrews[3] (Georgia Dept of Pub Health) Of the various anthelmintics carbon tetrachloride is the most effective and *convenient* for treatment of ankylostomiasis It is *commonly* used in 3 to 4 cc doses *for adults in water* milk or capsules either with or followed by saline purgation Acting directly on the worms, it removes 95 99 per cent of the type found in this country and completely *defaunates 60 90* per cent of *cases with a single treatment* Carbon *tetrachloride* used in this manner may in rare instances be toxic producing severe liver injury and death When toxic symptoms occur diets rich in carbohydrates and calcium and poor in fats and meats should *be used* and under *emergency* conditions calcium and sugar should be given parenterally

Two other circumstances may cause complications when carbon tetrachloride is used The first is consump

(2) New England J Med 2 7 701 703 Nov 5 1942
(3) Am J t M d 17 891 901 Decembe 194

disease With few exceptions the dose of sulfaguanidine was 0 1 Gm per Kg body weight initially and 0 3 Gm per Kg daily divided into six equal parts The dose of succinylsulfathiazole was 0 25 Gm per Kg body weight initially and 0 25 Gm per Kg daily divided into six equal parts given every four hours Duration of sulfonamide therapy varied from 2 to 14 days but most of the patients were treated for a period of 6 days

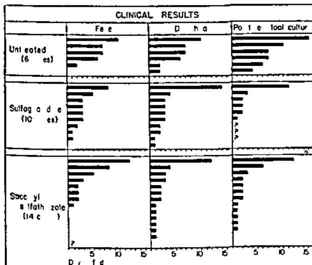


Fig 107 —C mp ison of li i l e ults in u t ted ulf gu nidine-tre ted d uc yl ulf th le-t eated O d t a f di rrhea que t n m k ind cates inad qu t d t

Consideration of treatment results is limited to the 26 proved and the 2 probable cases Six of the patients were not given the sulfonamides 10 were given sulfaguanidine and 14 were given succinylsulfathiazole Clinical results are summarized in Figure 107

Of the six patients who received no sulfonamide five had proved cases and one a probable case There were four deaths necropsy in two of these cases disclosed severe hyperemia multiple petechial hemorrhages and

Acute Bacillary Dysentery (Flexner) C J Smyth M B Finkelstein S E Gould (Eloise Mich) T M Koppa and F S Leeder[4] (Lansing Mich) report results of treatment with sulfaguanidine and succinylsulfathiazole in patients in a large state institution Distribution of cases by dates of onset is shown in Figure 106 The facts that most cases occurred in one building and that the outbreak did not have the explosive character of milk or water borne outbreaks indicated that food was the source of infection A survey of 328 food hand

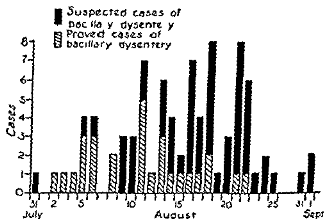


Fig 106 —Distribution of cases by date of onset indicates occurrence of suspected and proved cases

lers disclosed two with Bacterium flexneri in their stools

Eighty six patients were isolated for observation during the epidemic and in 26 cases diagnosis was proved by stool cultures In two additional cases there were negative stool cultures but these were considered probable' cases Treatment consisted in routine administration of camphorated tincture of opium and bismuth subcarbonate and when indicated dehydration was controlled by parenteral fluids Twelve patients were given sulfaguanidine and 24 succinylsulfathiazole These drugs were usually started on the first or second day of the

(4) J A M A 1 2 23 5 1330 Ap 4 1943

showed that water supply could not have been the source of infection Ice cream was rarely eaten by the attacked families and commodities were purchased from stores so widely distributed as to make it unlikely that they were the cause of the epidemic

The clothes of several gypsy families were washed in the home of the mother of the first victim a child who had played around the gypsy camp Among the clothes washed were those of a 3 year old child reported to have had dysentery and recovered Flies were abundant in the three communities most of which had open privy vaults there was but one effectively screened house Moreover most of the families attacked were related and visiting between them was common so the dysentery spread rapidly One factor common to the three communities was attendance at the carnival.

Of the 117 patients 72 were males and 45 females Gross fatality rate was 10 3 per cent the rate among males was 12 5 per cent and among females, 6 6 per cent. Ten of the deaths occurred in children under 10 (8 boys and 2 girls) All deaths occurred at the two extremes of life Further epidemiologic and immunologic studies are needed to determine whether males are more frequently infected and/or more susceptible

Increasing Incidence and Complications of Chronic Bacillary Dysentery Daniel N Silverman and Andrew V Friedrichs[6] (New Orleans) report that surveys have disclosed the endemic nature and constantly increasing prevalence of sporadic bacillary dysentery not only in and around New Orleans but also in many other states including New York New Jersey Illinois California Vermont Missouri and Virginia In their experience the prevalent bacillary strain has been the Duval bacillus the Flexner strain and at present the Shiga strain. The infection is more virulent than in previous years

This increase in incidence and virulence merits serious consideration in view of the aggregation of large numbers of men in the camps and various communities

6) New Orleans M & S J 95 401 407 Mar 1943

shallow ulcerations throughout the descending colon and rectum Bacterium flexneri was cultured from the ulcers in both cases One of the two patients who recovered was subsequently treated with succinylsulfathiazole to effect sterilization of the stools

The 10 patients treated with sulfaguanidine included 9 with positive cases and 1 with a probable case In seven the temperature returned to normal after three days of therapy one patient remained febrile for eight days One death occurred in a patient first treated on the sixth day of dysentery Necropsy disclosed ulceration and hyperemia of the colonic mucosa cultures of these lesions were negative Diarrhea was controlled in 8 of the cases after three days of therapy One patient who continued to have diarrhea was subsequently treated with succinylsulfathiazole

One death occurred among the 14 patients treated with succinylsulfathiazole Duration of fever in this group was comparable to that among the sulfaguanidine treated group Diarrhea was controlled in 11 of the cases after three days of therapy

The authors stress the importance of repeated stool cultures for at least three weeks after therapy has been discontinued Because succinylsulfathiazole is as effective as sulfaguanidine and because it is without the potential toxic effects of sulfaguanidine the authors believe that it is the drug of choice in acute bacillary dysentery (Flexner) It may also be of value in other types of bacillary dysentery

Rural Shiga Dysentery Epidemic F W Caudill, R E Teague and J T Duncan *(Louisville) report* an epidemic of 117 cases of Shiga dysentery in Adair County Ky occurring during June July and August 1941 The dysentery spread to 59 families grouped in three distinct communities

The infection was traced to a band of gypsies encamped near a carnival It was spread by direct contact and lack of environmental cleanliness Investigation

(5) J A M A 119 140 1406 Aug 2 194

ateness in view of the menace to the health of the civilian population by the soldier carrier returning from the heavily infected combat areas —Ed]

DOSAGE OF SULFONAMIDES IN TREATMENT OF BACILLARY DYSENTERY

DRUGS AND AUTHORS	INITIAL DOSAGE	FIRST MAINTENANCE DOSE	SECOND MAINTENANCE DOSE FOLLOWING IMPROVEMENT
Sulfathiazole			
	1 Gm for infants under 1 yr 2 Gm for infants over 1 yr	0 25 Gm. q 4 hr	
Tudor Cooper *et al*	1 gr /lb	2 gr /lb divided in 6 equal doses q 4 hr	
Sulfaguanidine			
Marshall *et al* Hall Lyon	0 1 Gm /Kg	0 05 Gm /Kg q 4 hr	0 05 Gm /Kg q 8 hr
Sulfasuccidine			
Poth *et al*		0 5 1 Gm /Kg divided into 6 equal parts	

Incidence of Amebiasis Observed at a Chicago Hospital over a 12 Year Period Marion Hood[8] studied the incidence of amebiasis in 1 999 patients and employes of the Research and Educational Hospital from June 1930 to June 1942 and found that an average of 7 9 per cent harbored amebas Even though the high incidences of epidemic years were included this average is below that generally quoted for the United States (10 20 per cent) Routine examinations of 103 normally well persons showed about one half the incidence of amebiasis demonstrated in a group of 243 patients with gastro intestinal symptoms Incidence of Endamoeba histolytica infestation increased markedly in 1933 1934 the period of the Chicago amebic epidemic In 1938 1939 incidence decreased to 4 per cent which appears to be normal for the population under consideration

(8) Am J T p Med 23 3 7 33 M y 1943

for the possibility of the infection spreading from a local community to one of the camps is great Vigilance should be observed and rigid isolation instituted in all cases discovered

Cases illustrating complications of chronic bacillary dysentery are reviewed Some of these complications are serious and may occur when least expected as in cases with mild symptoms Among these is perforation of th colon This finding is definitely in contrast to the earlier concept that the infection involved only the superficial mucosa of the bowel The deeper penetration of the bowel may be localized as to the cecum, but in some instances a large segment of bowel may be so involved in an ulcerative and gangrenous process that an entire section of the colon will slough completely A complication less serious than perforation is intense localized obstructing colonic spasm causing persistent and severe local pain This phenomenon is believed to arise as the result of a vasomotor reaction elicited by the dysentery organisms and is considered a manifestation of bacterial allergy Immediate relief is obtained with antispasmodics this should be followed by autogenous vaccine therapy for desensitization

Chemotherapeutic Aspects of Bacillary Dysentery Erwin Neter[7] reports that the clinical results obtained from use of sulfathiazole sulfaguanidine and sulfasuccidine are good particularly in acute bacillary dysentery Favorable results have been reported in dysentery caused by Shiga Flexner Sonne and Schmitz dysentery bacilli The drugs may be of value also in subacute or chronic dysentery Sulfasuccidine seems to be particularly promising The dosage of these drugs as recommended by different authors for treatment of patients with bacillary dysentery and carriers is summarized in the table on page 707

[The curative and prophylactic effectiveness of the sulfonamides has been conclusively demonstrated in civil and military medical practice This therapeutic weapon is of timely appropri

(7) G st oente ology 1 471 489 M y 1943

Primary infection appeared in four children aged 8 10 years in the form of subacute afebrile enteritis with frequent stools which disappeared spontaneously after several weeks Symptoms seem milder in children, consisting chiefly of digestive disorders anorexia indigestion diarrhea urticaria or general apathy The parasite often disappears at puberty

In adults lambliasis usually appears as the less grave forms of dysentery followed by diarrhea Prognosis is good even without treatment Diarrhea changes gradually into chronic enterocolitis

The various forms in which intestinal lambliasis is manifest are (1) fermentative dyspepsia characterized by pasty acid stools (2) enterocolitis with constipation followed by intense diarrhea meteorism abdominal pains and stools containing mucus (3) gastric functional disorders manifested by heaviness in the epigastrium nausea and postprandial somnolence

The presence of lambliae in the bile is frequently followed by inflammation of the biliary tract resulting in cholecystitis which may take various forms (1) spastic cholecystitis characterized by paroxysms of pain in the gallbladder region (2) catarrhal cholangitis with functional digestive disorders caused by mucosal bile thick with lambliae (3) chronic cholecystitis with secondary infections

Symptoms of toxemia at the level of the duodenum and jejunum may arise Infection may be accompanied by fever and an elevated white cell count. In one case in Dreyfus series polyneuritis was present accompanied by psychic disturbances loss of memory and speech difficulty Neurovegetative disorders such as brachycardia hypotension and palpitations may occur Nutritional disorders revealed by persistent loss of weight are frequent Generalized or localized allergic reactions may be provoked by lambliae The liver is most frequently exposed to the action of the parasite Hepatic insufficiency is often observed in enteritis manifested by catarrhal jaundice Secondary anemia is usually the

Clinical Observations on Lambliasis Philippe Renaud Dreyfus[9] (Lausanne) makes a report on 16 cases

Lamblia intestinalis formerly regarded as a rare harmless, exotic parasite, has been found frequently on duodenal intubation Not only the intestinal and biliary

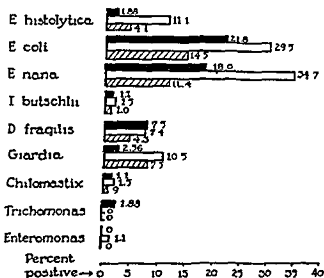


Fig 108 —P otozoa f und on rout ne e mination at an Illi ois nd a Pen syl ania institution (Courtesy D H W n l h, R M Stabler and J H Arn tt) (Hood, p 707)

tracts but also the nervous system, hepatic parenchyma and reticulo-endothelial system may be involved. Al though lambliasis manifests itself in various forms, cer tain factors are common to all—long duration tenacity, resistance to ordinary therapeutic measures and sensi tivity to atabrine and acranil. Repeated attacks of cholangitis or enteritis occur in patients between 20 and 30 years of age

(9) Gastroenterologia 66 3 S 34 194

days Adults were given 1 tablet three times daily for the same period. This therapy was repeated after several days interval Relapse occurred in only two infants who were cured by an additional five day treatment Chronic diarrhea and the slight degree of anemia in children and diarrhea giddiness loss of energy anorexia, headache and epigastric discomfort in adults disappeared. General nutrition of the children improved.

The authors conclude that the high frequency of Giardia lamblia in stools of the patients with long standing diarrhea and the favorable effect of treatment suggest that this organism may have been responsible for the acute enteritis in the nursery Further observations are needed to establish the exact degree of pathogenicity of giardia in man

Problem of Lambliasis P H Rossier and M Dressler[2] (Univ of Zurich) state that demonstration of Lamblia intestinalis can be successful only when certain technical prerequisites adapted to the peculiarities of the organism are fulfilled The pathogenicity of lamblia cannot be denied although it exists as a harmless saprophyte in the human organism and its pathogenicity is only facultative The fact of pathogenicity is strongly supported by disappearance of the lamblia on treatment with specific drugs (atabrine quinacrine and acranil) In the individual case the decision whether or not the symptoms are produced by the parasite may be rather difficult Although in presence of an intestinal or hepatic syndrome lambliasis should be considered in differential diagnosis no case even in the presence of lamblia should be viewed uncritically This does not however minimize the problem of lambliasis The authors suggest that in every case in which lamblia has been demonstrated with or without accompanying symptoms specific treatment be instituted for under certain circumstances as diminished resistance and preceding illness the harmless parasite may suddenly become pathogenic To prevent reinfection after a completed course of treatment other

(2) S hwei med W hn chr 73 09 1 F b 13 1943

only effect observed from parasitic action on the blood.

Since 1936 treatment of infection with Lamblia intestinalis has consisted of specific medication atabrine and acranil Oral administration of 0 25 gr of either drug is usually sufficient Results were negative in only one patient treated Most authors have obtained 100 per cent cures Reinfection is possible however

Enteritis in a Nursery Home Associated with Giardia Lamblia A prolonged outbreak of enteritis associated with Giardia lamblia affecting both children and adults in a British nursery home for evacuees is reported by G Ormiston, Joan Taylor and G S Wilson[1]

Between July 1940 and January 1941 28 of 31 infants and 16 of 20 adults were affected In the infants the first symptom was loose stools These were followed by repeated vomiting dehydration loss of appetite and weight and occasionally a temperature of 100 F In some cases acute symptoms were preceded by mild diarrhea The course lasted from a few days to a month. There were two fatal cases The adults were usually seized with a sudden acute and violent attack of diarrhea accompanied by severe abdominal pain Loose stools and vomiting followed. Additional symptoms were giddiness loss of energy weakness or faintness anorexia headache, nausea flatulence backache and fever Each adult had one to three attacks before treatment the interval between attacks varying from four to eight weeks Convalescence was usually rapid

Bacteriologic examination of the stools revealed that bacteria were probably water borne Giardia lamblia was present in 71 per cent of children and adults having loose stools at examination and in 32 per cent of those with normal stools The organism was found in 82 per cent of children and adults with a several months history of intermittent or continual loose stools and in 25 per cent of those without such a history

Infants under 2 years of age were given 1/6 of a 0 1 gr tablet of quinacrine three times daily for five

(1) Brit. M. J 2 151 154 A g 8 194

tion Placing the hand on the abdomen causes the pa tient to wince with pain this degree of tenderness is never seen in amebic dysentery In bacillary dysentery one can palpate the spastic and contracted large intes tine which feels like a rubber band or tube especially is this true of the sigmoid colon, which is acutely tender In the more chronic forms of dysentery particularly the amebic there may be isolated tender areas

Bacillary dysentery may be divided into mild acute toxic or fulminating and chronic forms In the mild form diarrhea lasts for 48 hours with blood and mucus Flexner s or Sonne s bacillus can usually be isolated Infections with Shiga s bacillus are as a rule more se vere The fulminating form is so acute that death may occur in 48 to 56 hours after onset The stools contain dark clotted blood with a peculiar musty odor when green sloughs are visible the prognosis is serious One of the fatal signs is hiccup

Statistics on geographical distribution of bacillary dysentery are often unreliable The important feature is that it occurs in epidemics with definite seasonal in cidence. There is considerable evidence that the disease is spread by house flies bacilli having been found in their intestinal tracts but no real evidence that it is carried by water

Complications are characteristic Conjunctivitis oc curs about the tenth day and iritis about the second week. Dysenteric arthritis associated with pyrexia and rigors also occurs Sometimes it is confused with the gonorrheal form but as a rule the former clears up quickly and does not leave much disability During World War I paroxysmal tachycardia occurred in con valescents probably due to action of dysenteric toxins on the heart muscle

Treatment for bacillary dysentery should begin as early as possible When the patient is being transported long distances morphine or tincture of opium may be given to keep him quiet and to stop violent peristalsis dysuria and tenesmus Saline treatment introduced by

members of the family should be investigated for lamblia Children, and some adults, should be taught to use the same precautions as in oxyuriasis i e avoiding soiling of the hands during and thoroughly washing the hands after defecation

[This and the preceding articles and numerous other contributions of similar tenor coupled with our own experience leave no room for doubt that the traditional concept of nonpathogenicity of Giardia lamblia is in need of revision. Obscure abdominal complaints, diarrheas cholecystitis simulating disorders asthenia and even prolonged fevers have been found by us to be due to this organism. Its rapid and complete elimination by atabrine usually led to prompt recovery in such cases —Ed]

Dysentery and Diarrhea in Wartime According to P H Manson Bahr [3] the most important type of dysentery in wartime is acute epidemic bacillary dysentery next comes the protozoal type

Dysentery bacilli disappear so quickly from the stools that difficulties in diagnosis arise Laboratories should be placed as near the front as possible so that when a patient arrives at a casualty clearing station or a stationary hospital diagnosis can be made at once and measures administered to save his life Out of every hundred persons affected about 20 become carriers for several months thus being the starting point for fresh epidemics.

Bacillary dysentery begins suddenly and is acute and toxic Shiga s bacillus produces a virulent endotoxin. The bacilli occur commonly only in the large intestine A dysentery of sudden onset accompanied by fever is probably bacillary and not amebic The latter is usually afebrile as Endamoeba histolytica produces a cytolysin but not a toxin Vomiting often occurs in bacillary dysentery but does not take place in the amebic form In the former after the initial diarrhea blood stained mucus is passed in quantities generally the patient loses sphincteric control Rectal tenesmus and dysuria are urgent owing possibly to spread of inflammation to the urinary bladder The pulse is rapid and the tongue furred Weight loss is considerable owing to dehydra

(3) Brit M J 2 345 348 Sept 19 374 376 Sept

of Endamoeba coli which are also found in stools Some times cysts with four nuclei are present in patients without symptoms of acute disease They are known as cyst passers or carriers

In treating acute amebic dysentery when the parasite is active in the stools and blood and mucus are being passed emetine is the drug of election but it does not fulfil all claims made for it The dose for an adult is 1 gr a day or 0 04 mg per Kg body weight It is given for 10 days and no longer as it is toxic It may affect the myocardium especially in children produce neuritis and cause scaling of the skin and cracked nails if not used with caution Emetine injections will not eliminate cysts from the stools for this purpose emetine bismuth iodide orally 1 gr as the first dose and 2 gr as the second dose is effective Doses larger than 2 gr need not be given The total amount necessary to cure amebic dysentery is about 18 to 20 gr The drug must be given last thing at night and preceded by a sedative the best being luminal An adjunct to this treatment is a quinoxyl retention enema given in the morning At the end of 10 days treatment the patient may eat any diet he prefers The ulcers heal in 10 to 12 days

[A timely contribution by a distinguished authority on tropical diseases and author of a well known text on the subject —Ed]

Treatment of Intestinal Disorders in the Military Forces is discussed by L C Gatewood[4] (Chicago) In World War I dysentery appeared in Germany in 1914 and headed the list of infectious diseases with 155 000 cases The British Army in France presented its maximal incidence in September 1916 with 126 cases per 100 000 but in Mesopotamia the incidence reached 2 900 cases per 100 000 In the East the frequency of the Shiga and Flexner types was about equal whereas in the West the Flexner type made up 85 per cent of the total.

In World War II in most zones bacillary dysentery will probably be the chief source of intestinal disability the predominating type varying in different locations

(4) Am J Digest D s 9 359 361 N embe 194

army surgeons 300 years ago, has still the greatest vogue Large doses of the salts are given Manson Bahr prefers sodium sulfate 1 drachm every 3 hours for the first 48, then four times daily till the stools become feculent

Dysenteric patients should not be starved but can be given junket jellies beef tea chicken broth and ice cream The fluid intake should consist of 4 to 6 pt lemonade or barley water Milk should be given moderately as it clots *and curds are difficult to pass* Arrow root is beneficial the addition of brandy is stimulating and comforting Blood transfusion is an excellent measure in desperate cases, as shown recently in an extensive outbreak in Poland The alternative measure is intravenous injection of hypertonic saline solution with 5 per cent glucose Objections to antidysenteric serum are *recorded, among them difficulties of administration and* reactions Most patients recover without serum but it may be used in toxic cases

Chronic bacillary dysentery is difficult to treat The best method is irrigation of the large intestine with 1 part eusol to 5 parts water

Treatment of both acute and chronic stages of bacillary dysentery has been transformed by the introduction of sulfaguanidine The drug is given in doses of 6 to 9 Gm daily for the first five days

Amebic dysentery as a dangerous condition has been overemphasized Endamoeba histolytica produces ulcers of the large intestine but apparently there is a struggle between processes of repair and destruction Although these lesions are scattered throughout the length of the intestine the intervening mucous membrane is normal

The disease is water borne Incubation period varies from 2 weeks to 120 days Varying clinical pictures appear Most cases are chronic and sigmoidoscopic study is often necessary for correct diagnosis Patients generally suffer from flatulence abdominal pain and periods of constipation *alternating with diarrhea The cysts* which are found in the chronic stage have four distinctive nuclei, but they must be

Malarial dysentery is common in tropical areas and may resemble cholera in its severity As a rule it is effectively treated with quinine Both atabrine and plasmoquin have been found effective

The diarrheas of schistosomiasis and of the later stages of leishmaniasis are most effectively treated with antimony in one of its various forms This drug is effective as an antiprotozoal agent only by the parenteral route When given orally it causes nausea and vomiting and is slowly absorbed When given parenterally it is as a rule completely excreted by the kidneys in three to five days Toxic symptoms which may occur include the rather prompt development of an irritating cough and the not infrequent occurrence of a type of pneumonia which is recognized pathologically as due to the drug and not a complication of the primary disease Other toxic symptoms may include joint pain or acute arthritis liver damage and cardiac manifestations especially bradycardia In some regions serious intoxication has been reported in as many as 15 per cent of patients treated with this drug

The Clinical Features of Intestinal Bilharziasis (Schistosoma Mansoni) are described by M Gelfand[5] (Salisbury Southern Rhodesia) Bilharziasis has long been regarded as a disease producing localizing signs in the bladder or bowel However practically any organ of the body may be affected. The ova settle in numerous places and the toxins from the parasites result in general or constitutional upsets in addition to interference with the local function of the affected organ Failure to recognize these constitutional signs has resulted in many cases passing unobserved There may in fact be no localizing signs or they may be so mild as to pass unobserved by the patient This applies particularly to mansoni infections

Perhaps the earliest symptoms of intestinal bilharziasis are seen in the invasive stage of the disease when the cercariae are still in the blood stream This

(5) Cli P oc C petown P st-G d M A 1 247 25? A gust, 1942

and possibly in the same location at different times The outstanding advance in therapy has been the introduction of sulfonamides, especially sulfaguanidine It is as yet too early to evaluate this drug Reports thus far indicate that it is more effective than any of the drugs previously available and less toxic than most of the other sulfonamides Reports are not yet available on the results obtained with sulfasuccidine

Of the protozoal diarrheas that due to Endamoeba histolytica is the most prevalent and important Conditions encountered in field service are especially favorable for development of severe dysenteric manifestations In this type of case emetine is a highly effective remedy but of all amebacidal agents it is the most toxic Dosage should be limited to 1 gr per day and not more than 12 gr should be given in one series or in any period of a month Emetine is a cumulative poison only slowly excreted and its greatest danger lies in its effect on the myocardium where it causes acute degenerative changes Evidence of renal or myocardial disease contraindicates its use Less serious but nevertheless unpleasant is the effect on the locomotor system resulting in paralysis of the legs and less commonly of the arms

The drugs of the arsenical group including carbarsone acetarsone or stovarsol and treparsone are effective amebacidal agents While far less dangerous than emetine their use is still associated with the risk of arsenical intoxication The symptoms are those common to other forms of arsenic poisoning and include renal hepatic and dermatologic manifestations The drugs of the iodoxyquinoline group (vioform chiniofon diodoquin etc) have proved especially valuable in amebiasis because they are practically free from toxic effects

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(5) Clin Proc Capetown Post Grad M A. 1 247 52 August 1942

occurs usually within a few weeks after original exposure to infection. The most important symptoms are urticaria, pyrexia and a high blood eosinophilia. Later, certain general symptoms may appear, but at this stage although ova are to be found in the stools there are no bowel disturbances that might be observed by the patient. The most important of these general symptoms are early weight loss, which may be extreme, and anorexia. Indigestion associated with pain and flatulence may occur, and these symptoms may simulate peptic ulcer or chronic cholecystitis. Marked myasthenia may occur, as may an irregular and mild pyrexia.

In a second clinical variety bowel symptoms are the main complaint. There may be well marked presenting symptoms such as abdominal pain, diarrhea or even the passage of blood or mucus in the stools. Periodic attacks of mild diarrhea have usually occurred over a long period. True dysentery is exceptional. In a few cases constipation may be the chief complaint. If repeated stool examinations for ova are negative in these cases a sigmoidoscopic examination should be made. The bowel lesions will be recognized as small hemorrhagic foci. Careful scrapings of these areas may result in the finding of the lateral spined ova.

A third clinical variety has its onset 10-30 years after the primary infection. It may, however, occur earlier. This group may be subdivided into two main types. In the first, hepatic lesions result from ova in the liver. Repeated attacks of transitory jaundice resembling catarrhal jaundice or infective hepatitis precede the development of cirrhosis of the liver. It is important to institute treatment in these cases before the symptoms of cirrhosis appear. The second type is associated with the development of general debility, predisposing the patient to deficiency disease or infections such as pneumonia or pulmonary tuberculosis.

Pre Eminent Importance of Clinical Signs in the Diagnosis of Intestinal Obstruction in Early Infancy. *In making a diagnosis of partial intestinal obstruction*

in infants radiographic and fluoroscopic barium studies are helpful but evidence from such studies is not always conclusive Harold Stadler[6] (Iowa City) reports two cases which illustrate that the gastro intestinal tract may appear normal by visualization studies even when clinically demonstrable partial obstruction is present One of these is presented

Girl born March 12, birth weight 7 7 lb did well for six days and then began to vomit frequently The stools had changed from the meconium type, and five yellow ones had been passed Vomiting increased in severity and persistence and the vomitus became bile stained At 7 days one apparently normal bowel movement occurred Subsequently peristaltic waves were observed to pass from left to right in the gastric area and from right to left just below the umbilicus Fluoroscopic studies the following day disclosed no evidence of obstruction But since vomiting and visible peristalsis constituted evidence of probable obstruction exploratory laparotomy was performed March 22 The peritoneum was opened under local anesthesia through a right rectus incision A moderate amount of free peritoneal fluid was present, and the stomach was much dilated An abnormal condition was noted in the duodenal area The relationship between the structures in the region was unusual with alteration in the customary course of the duodenum The exact nature of the abnormality could not be determined without risk of damage to blood vessels There appeared to be a zone of constriction in the region of the transverse me ocolon Posterior gastro enterostomy was performed and the infant s postoperative course was uneventful

In the second case a portion of the bowel in the region of the transverse colon was contracted In these cases it is possible that despite the partial obstruction vigorous peristalsis pushed the barium beyond the site of stoppage in a quantity sufficient to produce normal radiologic findings The clinical signs however constituted unequivocal evidence of obstruction

Intestinal Motility and Postoperative Distention Experimental and clinical studies on the motor mechanism of the intestine have produced a great volume of scientific literature and many important observations

(6) J A M A 1 0 1384 Dec 26 194

but much remains to be known Charles B Puestow[7] (Chicago) studied intestinal motility in a number of pa tients in whom surgical procedures exposed various por tions of the small and large intestine, permitting direct visual observation

A contrary motility between small and large bowel has been noted When the small bowel is vigorously con tracting the colon is inactive When the colon contracts the small intestine appears to be inhibited Drugs, in cluding opiates, physostigmine, prostigmine methylsul fate and the choline derivatives which stimulate motility of the small bowel inhibit the colon Solution of posterior pituitary and pitressin produce powerful contractions of the colon but diminish motility of the small bowel Postoperative distention may be due to paralyzing ac tion of morphine on the colon

The Medical Management of Intestinal Obstruction with special reference to use of the Miller Abbott tube is discussed by *Jarrett H Folley*[8] *(Dartmouth Univ)* Intestinal obstruction without strangulation may not be a surgical emergency Nonsurgical methods of decom pression done in conjunction with surgery have reduced mortality from 30 to 10 per cent or less

Wangensteen and others showed the importance of simple distention as the key point from which the sub sidiary physiologic and chemical changes of intestinal obstruction had their origin Abbott and Johnston dem onstrated that when distention was controlled and nutri tion maintained the patient could continue in good con dition almost indefinitely despite complete bowel ob struction It is the decompression of the distended bowel irrespective of the cause of distention that brings about the greatest improvement Realization of this factor is responsible for the great reduction of mortality in treat ment of intestinal obstruction

Relief of distention is *best accomplished by actual re* moval of the fluid and gas through intestinal intubation

(7) J A M A 120 903 908 Nov 21 1942
(8) New England J M d 8 606 61 M y

with the Miller Abbott tube This tube has two lumens *one connecting with a distensible rubber balloon and the* other available for aspirating intestinal contents If the tube is placed in the distal portion of the duodenum the balloon inflated and suction applied it will proceed to the point of obstruction in the paralytic type of obstruction it will be expelled by rectum As each segment of bowel is decompressed its motor activity returns and the tube is carried to the adjoining segment This method has many advantages Loss of fluid into the bowel lumen can be accurately measured and a like volume replaced The obstructive lesion can be definitely located and in many cases its nature can be determined It is possible to feed the patient withdraw the residue and thus maintain nutrition almost indefinitely This last factor makes the time of operation if at all necessary largely elective As the tube advances the patient may be fed progressively, clear fluids without milk hard toast cream cheese junkets jellies custards coffee sugar butter hardboiled eggs rice pureed vegetables and ground meat It is a simple matter to have the patient receive 1 500 calories daily on such a low residue diet Vitamin B complex and 75 100 mg daily of vitamin C are added and enteric coated salt tablets may be given to supply at least 5 Gm per L of intestinal contents removed

TECHNIC —*The technical difficulty encountered by many in* passing the tube has been the greatest objection to this method Also there has been some misunderstanding concerning the time involved in placing the tube in the small bowel Placing a tube in the stomach is always justified in any circumstance in which immediate operation is not indicated If after an hour or two of gastric decompression the patient is improving a longer wait is justified It may be 6 12 hours before the tube passes into the small bowel but so long as there is clinical evidence of improvement both subjectively and objectively one may wait longer Operation may however be indicated at any time during intubation—a problem that requires good clinical judgment

The first step is to anesthetize the nose with a long cotton swab soaked with 2 per cent pontocaine This is passed through the nares until its tip rest on the posterior pharyngeal wall

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(8) New E gl nd J Med 28 606-61° May 1

meters) is passed through the nose After a 15 minute wait the desired amount of air is injected into the balloon and the inflation tip is clamped The tube is then passed at the rate of about 15 cm an hour Progress should be checked daily by roentgenograms of the abdomen

Frequently the time factor is important, and passage of the tube under direct vision with the fluoroscope is desirable The tube may often be placed in the duodenum within a few minutes by this method following the same steps as before Another recently developed aid in the rapid passage of the tube is the stylet technic of Abbott (Fig 109) The wall of the aspirating lumen of the tube is pierced at the 50 cm mark with a length of 0 4 mm specially straightened stainless steel vom Hofe leader wire and the tip of the wire is advanced to a point 2 5 cm above the most proximal aspirating hole in the tube A loop is bent in the other end of the wire so that the tip cannot advance distally The terminal 15 cm of the tube will then contain no wire The tube is passed in the usual manner to the position shown in *A* With a temporary adhesive tape patch over the point at which the stylet pierces the tube wall 300 cc air is injected into the stomach and the tube is advanced until it lies along the greater curvature, as in *B* The tube is held at the patient s nose to prevent its slipping out and suction is applied to remove the air The stomach contracts as in *C* squeezing the tip of the tube ahead from position *1* to ~ The tip of the stylet then lies at *1* The antral spasm with concentric contraction distal to *3* prevents the terminal 15 cm from coiling and the stylet prevents coiling of the tube proximal to the antrum where the stomach is more flaccid The tip of the stylet is drawn back from *1* to *3* and by gentle steady pressure on the tube at the nose the tip is advanced from *2* to *4* The stylet is withdrawn the hole through which it was introduced is patched with thin rubber and, having inflated the balloon with 20 cc air the technic proceeds as usual

The tube may be left in place safely for many days and even weeks The possibility of erosion of the posterior pharynx or esophagus must be kept in mind however Such erosion is probably produced by too rapid removal of the tube Removal must be accomplished slowly and intermittently since pleating of the intestine will occur Considerable pressure may be exerted on the bowel wall in this manner For the same rea on the tube should never be taped or held in constant position while air is still in the balloon The pressure of the pleated bowel in such a case has caused multiple perforations

The swab is removed from the nose, and the tube well lubri cated with a water soluble gel is passed into the stomach Suction is applied and the stomach emptied

The patient is placed on his right side and the stomach dis tended with 200 to 300 cc air This step is necessary because of the reflex contraction of the antrum of the stomach in cases of intestinal obstruction The contraction converts the distal portion of the stomach into a narrow muscular organ and leaves a distended fundus into which the tube readily coils Distention of the stomach with air irons out the antral contrac

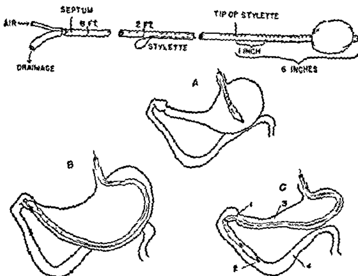


Fig 109 —T chnic of using stylet in p ng Miller Abbott tube

tion and allows passage of the tube along the greater curvature to the pylorus Enough slack is placed in the stomach to allow the tip to penetrate well into the duodenum The patient is left in this position suction is maintained and clear fluids without milk are allowed until the tip passes into the duo denum This is most readily identified by injecting air into the balloon If the balloon distends with little or no resistance, it is in the stomach A strong, steady resistance means that the balloon is at the pylorus The resistance in the duodenum comes and goes irregularly independent of respirations When this desired resistance is noted more tubing (several centi

dicitis there was rarely a primary epigastric component with secondary extension and localization of pain Nausea and vomiting were present in two cases without obstruction.

On examination localized abdominal tenderness was the chief finding in seven cases being acute in only two Rebound tenderness was noted in two cases and increased muscle tone in one In four instances a mass was found



Fig 110.—Appendix nd ep plo ppendages emoved t ope tion.

in the abdomen or in the pelvis Temperature in three cases was slightly elevated to 99 99 4 F Only two cases presented leukocytosis exceeding 10 000 per cu. mm.

At operation the typical finding instead of the pre operatively diagnosed conditions was a swollen blue black or hemorrhagic epiploic tag (Fig 110) generally attached in the sigmoid or the cecal region which on removal disclosed various degrees of degeneration gan grene inflammation or hemorrhage

Endometriosis F L Jenkinson and W H Brown[1]

(1) J A M A 122 344 354 J 5 1943

Surgical Significance of Epiploic Appendages Epiploic appendages are flattened projections of serosa enclosed fat found along the colon from the cecum to the lower portion of the sigmoid attached chiefly along the anterior taenia coli Their size varies from a few millimeters to several centimeters Blood is supplied by a single arteriovenous arcade

It is generally acknowledged that epiploic appendages frequently undergo torsion infarction and calcification, that they often produce symptoms closely simulating abdominal conditions requiring operation is appreciated less widely and that they occasionally initiate pathologic states incompatible with health or even life is generally overlooked H Martin Giffin Eugene P McManamy and John M Waugh[9] (Mayo Clinic) review 178 cases in which abnormalities of epiploic appendages were noted *The pathologic conditions* exhibited by the tags in order of frequency were necrosis degeneration or gangrene 65 cases calcification 39 inflammation 31 torsion 18 hemorrhagic infiltration 14 hyperplasia 3 cystic change 2 hyalinization 1 and carcinomatous implantation 1 Some tags presented more than one of these conditions

There were 10 cases in which the diseased appendages produced symptoms necessitating operation In five of these appendicitis was simulated and in one case each appendicitis or cholecystitis pelvic inflammation carcinoma of the sigmoid malignant disease in the upper part of the abdomen and intestinal obstruction Consideration was given to the symptoms and signs presented by diseased epiploic appendages in an effort to aid diagnosis The age range of the patients was 19 69 years The ratio of men to women was 6 4 Symptoms were acute or sub acute *in four* cases and chronic in six The most consistent complaint was pain which was present in all but the one case of chronic obstruction The pain tended to be mild and constant in five cases but in four it was severe and recurrent. *Contrary to what is found in typical appen*

(9) Arch S g 45 351 365 Septembe 1942

lence abdominal distention bloating and abdominal dis comfort Fourteen of the patients had exacerbations of bowel symptoms just before or during menstrual periods

There may be few significant physical manifestations depending on the location and extent of the lesion Sigmoidoscopic examination may reveal narrowing of the bowel lumen with intact but puckered red and con gested mucosa The mucosa is rarely sufficiently involved or ulcerated to make biopsy feasible When it is feasible it establishes a positive diagnosis and excludes carcinoma The intact mucosa explains the low incidence of gross or occult blood The concentration of hemoglobin may be decreased significantly depending on the severity and duration of associated menorrhagia

Positive roentgen signs depend on the extent of bowel involvement and the location of the lesion Implants on portions of the bowel which are freely suspended by a mesentery are less likely to have constricting lesions than are portions of the bowel which are extraperitoneal *and more firmly attached such as the rectum and lower* portion of the sigmoid colon Two factors probably pro duce obstructing lesions (1) the endometrial tumor which may involve the bowel wall sufficiently to com promise the lumen although the mucosa rarely is in vaded and (2) the intense inflammatory reaction which is the principal basis for roentgen findings This reac tion may result in fibrosis and cicatricial contracture of the bowel wall when lesions have been present for a considerable time although patients with definite con stricting lesions examined by the authors by barium enemas after surgical castration had almost complete restoration of the bowel lumen

Four of the 21 patients were given barium enemas (Fig 111) which demonstrated certain roentgen signs (1) A filling defect of considerable length involved ap proximately 4 7 in of the bowel lumen (2) A sharp de marcation of the filling defect was similar to carcinoma (3) Other portions of the colon showed little evidence of disease (4) Fluoroscopic examination and barium air

(St Luke's Hosp Chicago) stress the importance of endometriosis as a cause of constricting lesions of the rectum and sigmoid colon and discuss roentgen diagnosis The importance of correct preoperative diagnosis can not be minimized The lesions are often confused with carcinoma and patients sometimes are subjected to radical bowel resection whereas castration usually will suffice Frequently the condition may be regarded as inflammatory or infectious and be treated medically with little or no improvement

Endometriosis of the sigmoid colon or rectum resembles endometrial lesions elsewhere Implants usually occur on the serosal surface with subsequent involvement of the muscular coats The mucosa only occasionally is invaded An associated intense inflammatory reaction is always present Development of carcinoma from this lesion has not been recorded

About 25 per cent of all women with pelvic endometriosis have lesions of the rectosigmoid By combining this figure with the estimate that approximately 15 per cent of all women develop endometriosis, it may be concluded that 2-4 per cent of all women at some time during their active menstrual life may develop endometriosis of the sigmoid rectum or rectovaginal septum At this site it is a potential factor in causing a constricting or obstructing lesion of the colon and rectum Endometriosis of the rectosigmoid is important therefore in the etiology of constricting lesions of the rectosigmoid especially in women during their active menstrual life

The symptoms of constricting endometriosis of the rectosigmoid include menstrual abnormalities absolute or relative sterility and long standing bowel symptoms suggesting obstruction Weight loss or other evidence of ill health is seldom present The most frequent complaint of 21 patients with obstructive symptoms in the authors series was severe progressive constipation usually associated with pain low in the abdomen which was worse at menstruation one patient had small ribbon like stools associated with cramps Other symptoms [illegible] flatu

lence abdominal distention bloating and abdominal dis comfort Fourteen of the patients had exacerbations of bowel symptoms just before or during menstrual periods

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contrast films revealed an essentially intact mucous membrane (5) The involved portions of the bowel were relatively fixed and exquisitely tender to palpation during fluoroscopic examination

Endometriosis of the rectosigmoid should be differentiated most frequently from primary carcinomas of the



Fig 111 —Sp t film duri g fluoro copi examinati n to show inta t mucos

rectum and sigmoid colon or other infectious or inflammatory lesions It usually can be differentiated clinically from carcinomas by the younger age group (25-45 years) associated sterility and menstrual abnormalities absence of weight loss and anemia and the relatively long duration of symptoms Exacerbation of symptoms coinciding with the menstrual period is confirmatory evi

dence of endometriosis Carcinoma in contrast to the endometriosis is characterized roentgenographically by a short filling defect sharp irregular margins ragged moth eaten mucosa constant filling defect and usually absence of fixation or exquisite tenderness on palpation Infectious lesions usually may be differentiated clinically on the basis of fever leukocytosis weight loss anemia stool examinations and bacteriologic or serologic tests These lesions are characterized roentgenographically by a relatively long filling defect with ill defined irregular borders distorted mucosal pattern an indefinite line of demarcation between normal and pathologic portions variable filling defect influenced by medical treatment and considerable fixation and tenderness on palpation

Treatment of endometriosis of the rectosigmoid is summarized by Cattell who emphasizes the importance of conservative measures in patients under 35 whenever possible Radical treatment is necessary in most cases in which the colon and rectum are involved In such cases irrespective of age removal of both ovaries is necessary It is rarely necessary to resect the bowel Pemberton restricts roentgen therapy to patients of whom conservative treatment to preserve the child bearing function has failed

Roentgen examination of the colon by barium enemas is important following sterilization All patients in the present series had complete restoration of the bowel lumen when examined more than two months after surgical sterilization Palpation during the fluoroscopic examination demonstrates a freely movable colon without tenderness These findings differentiate endometriosis from constrictions caused by a malignant growth or inflammatory processes in which little or no improvement follows sterilization

Fat and Vitamin A Absorption in Sprue and Jejuno Ileitis David Adlersberg and Harry Sobotka (Mount Sinai Hosp New York City) discusses the possibility of

(2) G t terol gy 1 357 365 April, 1943

a functional differentiation between sprue and jejuno ileitis on the basis of fat tolerance and vitamin A tolerance tests Active sprue is characterized by a failure of absorption which manifests itself in complete lack of elevation of the lipids or of the vitamin A content of the serum after ingestion of a standard dose of butter fat or vitamin A, respectively However during a remission a fairly satisfactory fat and vitamin A absorption is found The nature of the impaired absorption in sprue is as yet unknown although there are indications that tropical as well as nontropical sprue and celiac disease are caused by deficiency of some essential dietary factor

In contrast to sprue cases of extensive granulomatous jejuno ileitis show a fairly satisfactory fat and vitamin A absorption with the tests Apparently small areas of nondiseased intestinal wall and possibly even the diseased areas are able to absorb fat and vitamin A, whereas in sprue there is a generalized inhibition of absorption in each individual cell of the intestine

The possibility of a functional differentiation between these two conditions is important While in typical cases of either disease the clinical picture the radioscopic and radiographic examination of the small intestine and the laboratory findings lead to a correct diagnosis in milder and borderline cases the differentiation may be difficult The tolerance tests for fat and vitamin A may prove helpful in this respect

Management of Ulcerative Colitis J Arnold Bargen[3] (Mayo Clinic) has classified ulcerative colitis into nine groups in seven of which the etiologic agent seems well established and in two (groups 2 and 3) of which the cause is unknown

Group 1 the commonest type variously known as colitis gravis and thrombo ulcerative colitis was formerly designated as idiopathic or nonspecific ulcerative colitis A characteristic streptococcus is considered the primary inciting organism This type is the most consistent and most typical clinically and pathologically and hence

(3) Gastroenterology 1 449-460 May 1943

proctoscopically and roentgenologically The intestinal wall is diffusely involved Earliest and severest manifestations appear in the rectum and lower segments of the colon The disease tends to spread diffusely upward until the entire colon and even the lower part of the ileum become involved Because of the consistency of this type of colitis other types will be described chiefly by noting in what respects they differ from it

Group 2 is used to designate chronic ulcerative colitis which differs pathologically from that of group 1 chiefly in that segments within reach of the proctosigmoidoscope are not involved in the pathologic process The existence and extent of the lesion are revealed by x ray The roentgen appearance of the diseased intestine may closely resemble that of any other form of ulcerative colitis or it may be different almost distinctive The lesion may be spread diffusely over the entire colon not including the rectum and sigmoid or it may be irregularly distributed and there may be relatively normal segments between those severely diseased No common causal agent has been determined for this form

The pathologic changes in group 3 are similar to those in group 2 except that the segments within reach of the proctosigmoidoscope are involved either alone or with segments of the colon above this level The cause is unknown.

In the last two groups there are no characteristic clinical features and the lesions are not distinguished from each other pathologically except by the distribution of the ulcerative process in the intestine It is emphasized however that successful treatment may be dependent on this division in many instances

Groups 4 and 5 are considered due to Mycobacterium tuberculosis and Endamoeba histolytica respectively

Group 6 is considered part of the syndrome of one of several forms of dietary insufficiency The rectal and sigmoidal mucosae appear diffusely hyperemic but except for tiny abrasions real ulcers are not present Roentgenologically the margins of the colonic mucosa

have a fine 'feathery' appearance, and puddling of the barium is apparent in segments of the small intestine Atonicity of the intestine is a striking feature

Group 7 is believed to be due to the virus of venereal lymphogranuloma The disease is practically always limited to the rectum and lower sigmoid colon

Group 8 is used to designate allergic colitis

Group 9 chronic ulcerative colitis may occur as a late phase of bacillary dysentery The patient's serum will agglutinate shigellae

Group 1 chronic ulcerative colitis has a definite cause and produces characteristic pathologic lesions and clinical symptoms Of prime importance in treatment is adequate rest As patients in this group are usually nervous and high strung control of their driving personalities becomes important Hospitalization for two to six weeks will tend to enhance subsequent therapy While the patients are in the hospital they should receive a proper diet and should rest and sleep at regular intervals Occupational therapy should be used and mild sedatives and antispasmodics administered The patients should be advised to try to avoid having bowel movements

Depending on the activity of the disease the diet will vary from nothing at all or merely clear fluids given orally to a high caloric diet rich in proteins and vitamins but low in residue In fulminating cases the patients are severely ill have a high temperature are severely prostrated and have bloody stools In such cases it is advisable not to administer any food or fluid by mouth during the acute phase Fluid balance can be maintained by parenteral administration of physiologic salt solution and a 5 or 10 per cent dextrose solution Blood transfusions may also be used It is advisable to give small quantities of blood at short intervals rather than large amounts at longer intervals In the average case 250 cc blood may be given daily or every other day for 4 to 10 days With subsidence of the acute phase fluids and low residue foods may be given orally The diet may be increased gradually until the patient is

receiving a basic diet that is a diet rich in proteins which will furnish about 2 300 calories daily This diet is further increased so that in the average case 3 400 calories are being given daily by the end of the second week This diet should contain 120 Gm or more of protein

Antistreptococcus serum (ulcerative colitis) administered intramuscularly or intravenously is indicated in cases in which the disease is severe or fulminating and ulcerative colitis streptococcus vaccine is indicated in cases in which the disease is less severe and in cases in which the serum has produced improvement The vaccine should be administered subcutaneously in increasing doses which never should be large enough to produce local or systemic reaction Administration of vaccine is continued for two to three months and usually produces slow but progressive improvement It is then discontinued for six to eight weeks whereupon it is resumed

To date azosulfamide has proved the most helpful of the sulfonamides used in this form of colitis From 50 to 90 gr divided into six equal doses is given each 24 hour period for 2 weeks The patient is allowed a rest of a week then azosulfamide is administered for two weeks Sulfaguanidine has proved helpful in some cases A total of 8 to 16 Gm is administered in divided doses each 24 hours A week s rest period is also advisable Sulfathiazole administered in the usual doses has proved valuable in some cases A recent drug which gives great promise is succinylsulfathiazole Bargen has found that 1 5 Gm every four hours for several weeks produces marked relief without production of toxic effects

The problem of when to use surgical treatment in this type of chronic ulcerative colitis frequently presents itself Bargen believes that ileostomy should largely be confined to cases in which such complications as polyposis rectal stricture extensive perirectal abscess and carcinoma are present and to the occasional cases in which the disease is intractable even though no apparent complications are at hand Ileostomy is unsuitable for

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Sanatorium care affords the only adequate treatment for tuberculous ileocolitis classified as group 4

A satisfactory treatment for the average case of amebic colitis (group 5) consists of 2/3 gr emetine hydrochloride administered subcutaneously twice daily until 4 gr has been given Carbarsone is given concomitantly 4 gr doses orally three times daily until 12 doses or 48 gr have been given During the next seven days an iodine preparation such as diodoquin or vioform is administered orally in 4 to 8 gr doses three times daily At the end of this period the course of treatment with emetine hydrochloride and carbarsone should be repeated A series of stools should then be examined for Endamoeba histolytica This course of treatment will be successful in most cases observed in the Middle West Except for supportive measures no other treatment is necessary

The major effort in treatment in group 6 should be directed toward establishing a diet rich in vitamins and proteins low in residue and furnishing a large number of calories

Sulfonamides have been helpful in relieving symptoms of the colitis due to venereal lymphogranuloma (group 7) Rectal dilatation or colostomy may be necessary because of rectal stricture

With regard to group 8 it should always be remembered that the patient with ulcerative colitis may also be allergic to foods drugs and other substances that the allergy should be treated but that only rarely is it the basic causative factor of the colitis

The treatment of chronic bacillary dysentery (group 9) will include various supportive measures antidysentery serums bacteriophages and sulfonamides Excellent results have been observed with the bacteriophage Of the sulfonamides the best results have been obtained with sulfaguanidine sulfathiazole and succinylsulfathiazole

[An a thor tat ve review by a colleague whose contributions to enterology are noteworthy and for whose therapeutic acc mplishments in this difficult field I can freely vouch —Ed]

fulminating or severe ulcerative colitis both because of its high mortality *in this type of the disease and because* of the unsatisfactory end results

Since the cause of group 2 chronic ulcerative colitis remains unknown treatment is naturally empiric Furthermore, since the disease involves intestinal segments above the reach of the sigmoidoscope since it is segmental in distribution and since radical removal can be effected without a permanent colonic stoma surgical resection seems to be the treatment of choice In many respects this disease resembles so called regional ileitis Perhaps it would be better to designate both diseases as regional enteritis It is unwise to operate when active inflammation is present or when associated toxic symptoms such as fever night sweats and progressive weight loss are present Surgery should be undertaken when the disease is relatively quiescent Furthermore surgical resection is not applicable in all cases Consequently treatment with succinylsulfathiazole or sulfaguanidine and the use of other supportive measures often help to control the condition However when active symptoms have subsided and the disease is limited to segments of the intestine which can be removed without particular interference with the bodily economy and with minimal risk resection should be performed

The cause of group 3 ulcerative colitis is also unknown therefore the differences between groups 2 and 3 are anatomic rather than etiologic Treatment is largely symptomatic Many of the measures outlined for group 1 have been used In many cases sulfonamides have produced satisfactory response Of these sulfaguanidine and succinylsulfathiazole have proved most satisfactory but in this type of colitis in particular no single therapeutic measure has proved satisfactory Consequently surgical treatment is used more frequently in group 3 than in group 1 cases and is similar to that used in group 1 cases It must be recognized, however that persistent proper management has resulted in control of the disease and possibly in ultimate healing of the intestinal lesions

the significance of glycosuria necessitates determination of the rates of glomerular filtration and tubular reabsorption as well as of blood sugar concentration

In the normal individual all three factors are normal In the patient with renal glycosuria or glycosuria induced with phlorhizin and probably in the patient with glycosuria of pregnancy the reabsorptive capacity is decreased In the patient with diabetes mellitus the blood sugar is high and the renal factors are normal In the aged person with diabetes and nephrosclerosis there may be a greater or lesser impairment of the functional units of the kidneys resulting in a decrease in filtration rate and hence in an increase in blood sugar concentration required to produce glycosuria (Fig 112)

Accordingly the concentration of sugar in the urine is not an index of the severity of the metabolic disturbance nor does it give any information concerning prognosis Once the renal factors are evaluated the amount of carbohydrate which the patient retains on a specific dietary intake can be determined and thereby an estimation of the severity of the metabolic disorder may be made

The Relation of Trauma to Diabetes is discussed by Elliott P Joslin[6] (Boston) The thesis that trauma de novo can cause diabetes has steadily lost support with the increasing knowledge of the nature of the disease However evidence has accumulated to show that trauma indirectly can activate or accelerate the appearance of a latent diabetes in the hereditarily predisposed particularly if accompanied by infection reduced muscular exercise gain in weight or overeating

Trauma in the course of diabetes has grown in importance because the duration of the disease has trebled thus lengthening the period of exposure Moreover the danger of exposure to trauma is intensified each successive year a diabetic lives because time is provided for the disabling complications of the disease to appear and the physical infirmities of the normally aging process to

(6) A S g 117 607 6 2 Ap 1 1943

DISEASES OF METABOLISM AND NUTRITION

Significance of Glycosuria I Arthur Mirsky and Norton Nelson[5] (Cincinnati) point out that recent studies in renal physiology have provided information that should clarify some of the misconceptions concern

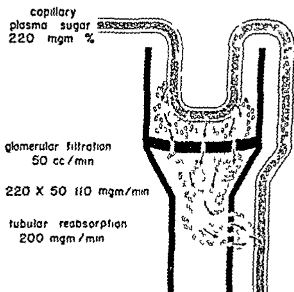


Fig 11[*]*—D abet s and n phros le e b orpti e capacity of tubules exceede d xte filtrati n rate (plasma sugar × filtr tion at) be ause of inadequate filtration th ough the abno mal glomerulus*

ing the presence of dextrose in the urine Excretion of dextrose is dependent on three factors blood sugar level rate of *filtration of dextrose by the glomeruli and rate* of reabsorption by the tubules Therefore glycosuria reflects not only the metabolic phenomena which produce hyperglycemia but the physiologic status of various *functional units of the kidney A proper appraisal of*

(5) Arch Int Med 1 8 7 83 June 1943

in the pancreas Total pancreatectomy in a dog invariably causes diabetes but that organ has such a high factor of safety that diabetes fails to appear if more than one fifth of the gland remains This fact shows how futile the attempt must be to connect bodily trauma with diabetes Moreover the pancreas lies in the depths of the abdominal cavity with the abdominal wall peritoneum and stomach in front of it is partly overhung by the liver and in close touch with the spleen and posteriorly is protected by the backbone It is hardly conceivable that four fifths of it could be destroyed and yet allow life to go on The discovery that insulin is manufactured only in the beta cells of the pancreatic islets made the evidence of the unity of diabetes complete

Subsequently the close connection of the pituitary gland with diabetes was recognized and later it was found that actual diabetes could be brought on by injections of an anterior lobe extract This suggested that the nervous system was independently involved and that diabetes was perhaps influenced both by functional and by organic insults to the brain Such suppositions however were soon dispelled when investigation disclosed that the diabetogenic action of the anterior pituitary extract lay in its power to destroy the beta cells of the pancreatic islets Thereby the unity of diabetes and its localization in the pancreas was again demonstrated The influence of the adrenal gland on carbohydrate metabolism has received emphasis but there is no known instance in a human being in which disease or injury of the adrenal gland has brought on diabetes

To prove that trauma causes diabetes one must show that the pancreas is gravely injured in fact at least four fifths or probably nine tenths destroyed or that trauma has so acted on the anterior pituitary as to cause it to discharge an excess of extract which in turn can destroy the insulin producing cells of the pancreas Examples of such events are almost unknown in human beings With respect to the pancreas there exist only the cases of Wells Stern and the two of Grafe which

advance In addition the tissues of a diabetic are more vulnerable than those of a nondiabetic Trauma may make the diabetes more severe but this effect is not necessarily permanent

To prove that trauma is the cause of diabetes in any case it must be shown (1) that the disease did not exist before the trauma (2) that the trauma was severe injuring the pancreas (3) that the symptoms and signs of the disease developed within a reasonable period after trauma the etiologic importance of the trauma waning with prolongation of the interval and (4) that the symptoms and signs were not transitory but permanent

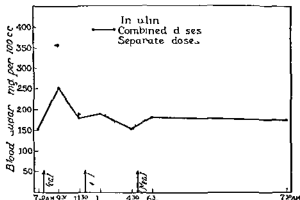
Proof of the diagnosis of diabetes is all important and is dependent on the demonstration not only of glucose in the urine but of a per cent of glucose in the blood of 130 mg or above when the subject has been without food for five or more hours or of 170 mg or more after the intake of food Glycosuria (nondiabetic) levulosuria lactosuria and pentosuria are harmless states The common tests for glucose in the urine are reliable and seldom subject to error but this does not hold true for tests of the blood sugar which are more complicated and to be diagnostic must be carried out with special precautions regarding technic and reagents The diet and physical status of the subject at the time of the examination are of prime importance else the reliability of the diagnosis is questionable

Whenever the question of trauma as the cause of diabetes or as an incident in the course of diabetes arises one should establish whether diabetes existed before the accident A rigorous search for symptoms and signs of the disease should be made as well as for the existence of factors predisposing to its development so that the date of onset can be determined with reasonable accuracy Predisposing conditions include age race positive heredity and most important of all obesity

Less and less credence has been given to the direct causation of diabetes by trauma since 1889 when it was demonstrated that its etiology and pathol ntered

was obtained It was found that the numbers of cases in which the diabetes was controlled satisfactorily with mixtures representing ratios of the protamine zinc insulin to unmodified insulin of 1 1 1 2, 1 3 and 2 3 were approximately equal

The authors also made a comprehensive study of the effects on diabetic patients of injecting various mixtures using two young women with severe diabetes as subjects No one ratio of protamine zinc insulin to unmodified in



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sulin gave an optimal effect However mixtures in which the ratios of protamine zinc insulin to unmodified insulin were 1 2 1 3 1 4 2 3 and 2 5 were capable of adequate control of the blood sugar during the 24 hours after injection Use of equal parts of the two insulins gave results similar to those obtained with protamine zinc insulin alone since most of the unmodified insulin was probably in combination with the excess protamine A mixture of 1 part protamine zinc to 5 parts unmodified insulin resulted in a marked immediate hypoglycemic effect such as might follow injection of a large dose of unmodified insulin alone

have gained general recognition as proving that injury to the pancreas leads to diabetes and not one of these cases is above criticism As for trauma to the pituitary leading eventually to diabetes the evidence is still less convincing and Rathery s recent description of an acromegalic with a complicated head injury is only remotely conceivable as an example of stimulation of pituitary remnants to excessive secretion As a matter of fact Rathery did not attribute the diabetes in this case which followed removal of an eosinophilic adenoma of the pituitary to the pituitary itself but rather to injury of the neighboring hypothalamic region

The possibility of diabetes arising from injury to the pancreas without external bodily trauma such as that pursuant on pancreatitis hemochromatosis cancer infections or injury to the nervous system must also be considered None of these situations has been shown to be the cause of diabetes It is recognized of course that latent diabetes may be activated by trauma particularly when the latter is associated with infection but in these instances it is the indirect effect of the accident rather than the direct trauma which causes the trouble

Clinical Experience with Mixtures of Protamine Zinc and Unmodified Insulins Alice G Hildebrand and Edward H Rynearson (Mayo Clinic) state that most authors agree that for satisfactory control of severe diabetes mellitus protamine zinc insulin must be supplemented by unmodified insulin Protamine zinc insulin supplies the patient s basal requirements while unmodified insulin is given to supply the additional need arising from ingestion of food The exact time and manner of administration of supplementary unmodified insulin have not been generally agreed on Also the question of which scheme of adjusting the amounts of each type of insulin gives the best results has not been answered

The authors reviewed the records of 100 cases of diabetes to determine which ratio or ratios had been most often arrived at in these cases when satisfactory control

(7) Arch Int Med 7 37-45 July 1943

strength prepared from insulins now on the market Undoubtedly any of these modifications result in a preparation which retains all the advantages of protamine zinc insulin and eliminates many of its shortcomings —Ed]

Control of the Hyperglycemia of Obese Diabetics by Weight Reduction L H Newburgh[8] (Ann Arbor Mich) describes the effect of weight reduction on delayed glucose utilization in 62 obese adults The glucose *tolerance tests became normal in 77 per cent of those* patients who were willing to undergo adequate weight reduction (see Table) Newburgh contends that the delayed glucose utilization encountered in obese adults is usually of a fundamentally different nature from that of diabetes mellitus Reasons for this contention are several

First the disturbance is mild often existing for years without causing symptoms despite lack of treatment Clinical acidosis does not occur Delayed glucose utilization is a common accompaniment of obesity having been observed by various authors in 50 to 65 per cent of obese individuals These investigations indicate that prolonged obesity usually causes changes in the organism one of which is delayed carbohydrate utilization The contention of some that obese patients with hyperglycemia are *diabetic would lead to the assumption that most persons* are diabetic this latter is not the case Further if these obese patients are mild diabetics whose inherited weakness becomes clinically apparent when their total metabolism is increased by the obesity then those whose inherent fault has become hidden again through weight *reduction should manifest their diabetic state when they* sustain infection Newburgh has observed only one instance of this type and in this case the urine remained sugar free despite the presence of a severe upper respiratory tract infection with chest pain bloody sputum and a temperature of 104 F Finally if the severity of diabetes is augmented by increased weight it should be possible to demonstrate this effect in the juvenile diabetic Newburgh attempted to do so in one case and

(8) An I t M d 17 935 94 D ember 194

Injection of the two types of insulins at separate sites was *not as* satisfactory as *their injection* together (Fig 113) *Following injection in separate sites a marked im* mediate hypoglycemic effect was obtained, but smooth control of the blood sugar level during the remainder of the 24 hours did not result

An attempt was made to eliminate the midmorning lag in hypoglycemic effect of the mixtures of the two insulins by injection one hour instead of one half hour before breakfast This method eliminated the lag but did not

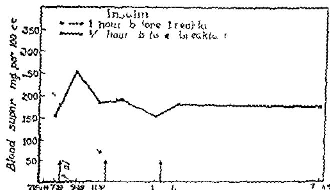


Fig 114 —Same case as preceding Comparison of blood sugar curves obtained after injection of mixtures of two types of insulin one hour and half an hour before breakfast

result in smoother control of the blood sugar during the remainder of the 24 hours (Fig 114)

[Simplicity is the keynote in the therapy of diabetes *The hope* that a single daily injection of protamine zinc insulin would constitute satisfactory maintenance treatment in nearly all cases has not been realized. In severe diabetes in particular *it is usually* not possible to give enough of the protamine zinc insulin to prevent postprandial hyperglycemia without provoking hypoglycemia during the *fasting hours of the night or early morning Hence the* numerous investigations of this nature in recent years MacBryde and Roberts (1943) feel that they have evolved a single maintenance *dose effective in most cases* This *consists of a modified* protamine zinc insulin with 2 parts prolonged action to 1 part of rapid action prepared by admixture of equal parts of protamine zinc insulin and regular insulin at pH 7 2 Colwell and Izzo (1943) on the other hand recommend a modification of 2 parts soluble insulin with 1 part protamine zinc insulin *both* *H.M.*

cent of adult obese hyperglycemics it is permissible to predict that thorough weight reduction of the obese members of the group will abolish the retarded glucose utilization in one third of the patients who are believed to have diabetes mellitus

Treatment of Diabetes Mellitus William H Olmsted[9] (St Louis) believes that if the diabetic patient receives a diet which fulfils the requirements for calories minerals and vitamins and is kept sugar free and if the obese diabetic patient reduces premature development of arteriosclerosis may be prevented and such persons may enjoy a normal life span Experience with forms of protamine zinc insulin which contain less protamine indicates that they are better adapted to treatment of diabetes than the forms of protamine zinc insulin now in use Finally success of the dietetic management of diabetic patients depends largely on methods of dietetic education Experience indicates that simple methods utilizing the kitchen measuring cup result in better dietetic control than use of the metric system despite the undoubted accuracy of the latter method

Coated Tongue Burrill B Crohn and Rudolph Drosd[1] (Mount Sinai Hosp New York City) were unsuccessful in an attempt to explain simple coated tongue on a basis of direct retrogression of gastric or intestinal material Although under exceptional conditions they were able to demonstrate the retrograde transport of colonic contents as far as the stomach success in even 4 of 10 experiments was dependent on certain experimental conditions Thus the alimentary tract of the subject under observation had to be cleansed and empty and at rest Only lithium carmine could be utilized for successful demonstration and that only in saline suspension Obviously these conditions are not often met in clinical observations Coated tongues occur in persons who have over loaded and abused their digestive tract rather than under conditions of austere fasting

(9) J I w M S 33 95 101 Ma h 1943
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found that a gain of 31 lb was without effect in lessen ing the patient s ability to dispose of glucose

A few of the obese hyperglycemics in this series were not improved by reduction *of weight to normal. One* explanation is that they have diabetes of the juvenile type It is also conceivable that the prolonged hyper glycemia caused organic changes in the islets of Langer

GLUCOSE TOLERANCE TESTS O 62 PATIENTS BEFORE AND AFTER WEIGHT PEDUCTIO I

	BEFORE				AFTER			
	Fast ing	1 H	2 Hr	3 H	Fast g	1 Hr	H	3 H
Full co operation								
Tests became normal (36 patients)	16	203	29	234	89	154	113	75
Tests became mark edly improved (patients)	19	3 8	390	2 7	102	212	173	116
Tests slightly or not at all improved (6 patients)	53	40	462	469	231	349	393	366
Av for group (47 patients)	177	310	3 3	68	110	184	154	116
Partial co-operation Tests improved (15 patients)	189	330	364	94	119	218	215	15
Full and partial co operation *Av for all patients*	*180*	*315*	*339*	*2 2*	*112*	*19*	*169*	*12*

hans since Best has shown that high blood sugars dam age the insular cells in dogs

During 1936 370 new patients were classified as diabetic after thorough study Of these 316 were aged 30 or more, and 57 per cent of these adults were obese *on* admission *Therefore approximately one half of the 370* patients *whose ages ranged from a few months to 71 years were obese when they were admitted Since experi ence has shown that adequate weight reduction will abol* ish lessened carbohydrate utilization in at 9 per

cent of adult obese hyperglycemics it is permissible to predict that thorough weight reduction of the obese members of the group will abolish the retarded glucose utilization in one third of the patients who are believed to have diabetes mellitus

Treatment of Diabetes Mellitus William H Olmsted[9] (St Louis) believes that if the diabetic patient receives a diet which fulfils the requirements for calories minerals and vitamins and is kept sugar free and if the obese diabetic patient reduces premature development of arteriosclerosis may be prevented and such persons may enjoy a normal life span Experience with forms of protamine zinc insulin which contain less protamine indicates that they are better adapted to treatment of diabetes than the forms of protamine zinc insulin now in use Finally success of the dietetic management of diabetic patients depends largely on methods of dietetic education Experience indicates that simple methods utilizing the kitchen measuring cup result in better dietetic control than use of the metric system despite the undoubted accuracy of the latter method

Coated Tongue Burrill B Crohn and Rudolph Drosd[1] (Mount Sinai Hosp New York City) were unsuccessful in an attempt to explain simple coated tongue on a basis of direct retrogression of gastric or intestinal material Although under exceptional conditions they were able to demonstrate the retrograde transport of colonic contents as far as the stomach success in even 4 of 10 experiments was dependent on certain experimental conditions Thus the alimentary tract of the subject under observation had to be cleansed and empty and at rest Only lithium carmine could be utilized for successful demonstration and that only in saline suspension Obviously these conditions are not often met in clinical observations Coated tongues occur in persons who have overloaded and abused their digestive tract rather than under conditions of austere fasting

(9) J Iow M So 33 95 101 M b 1943
(1) G t t l gy 1 34 43 J 1943

Although it is conceded that under certain circumstances the retrograde activity will transport the content of the rectal ampulla as far as the stomach the gap from stomach to tongue could not be bridged Under pathologic conditions of cardiospasm with esophageal retention the tongue is usually coated and the mouth odor fetid But this is a definitely pathologic mechanism and cannot in any manner alter conclusions and experiences under normal physiologic conditions

It is therefore considered that the coated tongue is an intrinsic lingual phenomenon Reflexly through the autonomic nervous system by means of deviations in vasomotor control the tongue reflects the state of hydration in the body the conditions of digestive activity in the alimentary tract and the general health of the individual The delicate filiform papillae act as the bellwether of the body politic raising themselves to gather mass and debris when all is not well and remaining smooth velvety and clean when conditions are appropriate for health and normal function

Precancerous Mouth Lesions of Avitaminosis B Etiology Pesponse to Therapy and Relationship to Intra Oral Cancer Hayes Martin and C Everett Koop[1] report on clinical material found among the general admissions to the head and neck clinic of the Memorial Hospital New York City including three special series of cases in which dietary surveys were made They conclude that degenerative mucous membrane changes are found in most cases of mouth cancer These changes usually result from a combination of several forms of chronic irritation (tobacco syphilis sepsis avitaminosis) The most frequent and probably the most important form of chronic irritation from the standpoint of carcinogenesis in the oral mucous membranes is that of avitaminosis B Most patients with mouth cancer have mild to marked avitaminosis B on admission This disorder tends to be aggravated by the necessarily restricted diet during the painful stages of the cancer

(1) Am J Surg 57 195 5 August 1942



Fg 115 —Ul at on f tongu in a t m B

Fg 116 (l ft) —P gr s d l pm t f d g t h g f t- m B lt fi lly n rot l t ng M 3 fi t e n Novem ber 1933 h d mild bu g e t t gu Th w n d fi te l f th to g d tu of d de ws t r gn d Sympt m t u d a d f w m nth l t mld fi mm t d h p rt ghy f p pll w t l C d t n w th n gn d p b bly d to di t y d fi en y d vit m n ther py w gi n

F 117 (ght) — S m c ht l te P t e t t d with t gu l f w ght th d m t l d p m ked p gre h g (t l to gu) Aft t k g 45 Gm gr l y t d ly f m th h g d 10 lb d th m t l dep d bject vmpt ms n t gu d pp ed

Supplementary vitamin therapy is one of the most important factors in successful treatment of intra oral cancer There is considerable clinical evidence that the mucous membrane lesions of avitaminosis B are not confined to the oral cavity but affect the whole gastro intestinal tract It is therefore possible that such degenerative changes are significant in the etiology of gastric



Fig 118—Perlè he in woman 6 wh had crusting and fissuri g at labial commissu es for one month also marked hypertrophy and agglutination of p pillae and fissure f ld ng of mucosa of tongue (scrotal tongue)

and intestinal as well as of oral cancer One of the most effective means of prophylaxis against mouth cancer reasonably appears to be an increase in the general vitamin B intake in foods

Feeding of Healthy Infants and Children Philip C Jeans (State Univ of Iowa) believes that despite all refinements of artificial feeding breast feeding remains an ideal procedure This is true despite the facts that human milk contains only a bare minimum of most nutritional essentials and that the body composition of the breast fed infant departs widely from that which preceded and that which follows

Vitamin D is needed early by all babies whether

( ) J A M A 1?0 913 9 1 Nov 1 1942

breast or artificially fed Vitamin C is needed early by artificially fed babies and is a harmless safeguard for the breast fed baby No need for vitamin A from special sources exists If current custom errs it does so in the direction of giving too much vitamin D and too little vitamin C and in not giving either early enough Supplementary foods should be given not later than 4 months of age to both breast and artificially fed babies One of their important functions is to supply iron and B vitamins

While observers do not agree too well as to the particular nutritional or dietary factors responsible for dental caries nearly all agree that one or more dietary components may be responsible Thus dental caries is the most widespread nutritional scourge

Three nutritional essentials deserve special emphasis in childhood vitamin D protein and calcium Vitamin D is required throughout the growth period which fact is extensively overlooked Milk the only constant good food source of calcium is not taken in sufficient quantity by many children Protein deficiency is much more common than is generally realized and a diet adequate in protein cannot be arranged without inclusion of milk Although insufficient thiamine is obtained by many children the remedy lies in better food selection not in thiamine medication Enrichment of flour and bread and decreased consumption of sugar should contribute materially to the desired end Vitamin A from special sources is not needed by the normal child A diet deficient in vitamin A is deficient also in other respects and the remedy is better diet not medication Anorexia and poor eating habits in older children often originate in mismanagement of feeding in infancy

Trace Elements in Nutrition Maurice E Shils and E C McCollum[3] (Johns Hopkins Univ) review the literature on the trace elements of nutrition and conclude that six—iron copper iodine manganese cobalt and zinc—are essential to animal life Knowledge of the re

(3) J A M A 1 0 609 619 O t 4 194

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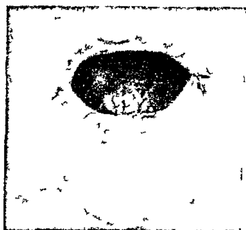


Fig 118—Pe lèche in wom n 6 wh h d crust ng and fissu ng t lab al omm ssures f n m nth also ma ked hyp rt phy and agglutination of papillae and fis ure fold ng f muc a of tongue (crotal to gue)

and intestinal as well as of oral cancer One of the most effective means of prophylaxis against mouth cancer reasonably appears to be an increase in the general vitamin B intake in foods

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Vitamin D is needed early by all babies whether

( ) J A M A 1 0 913 9 1 Nov 21 194

and fluid imbalances and deficiencies in the preoperative period has contributed directly to a lowering of surgical mortality and morbidity Once the patient has successfully weathered the operation and is out of the woods so to speak, we are not so concerned about metabolic abnormalities real or apparent On the other hand while we are not so mindful of the surgical risk in patients with duodenal ulcer undergoing resection the postoperative nutritional disturbances which often prove annoying and refractory do concern us Adequate daily caloric intake re enforced by parenteral administration of crude liver extract is essential to eventual recovery —Ed]

Total Gastrectomy Effects on Nutrition and Hemopoiesis J Matthews Farris Henry K Ransom and Frederick A Coller[5] (Univ of Michigan) studied the effects of total gastrectomy on nutrition and hemopoiesis in man Metabolic studies support the clinical observation that patients are able to maintain good nutrition following total gastrectomy Nitrogen excretion studies indicate that the stomach does not play an essential role in protein digestion and that this function may adequately be taken over by the trypsin of the pancreas and the erepsin of the small intestine Similarly determinations of the total fat in the dried feces indicate that there is no interference with fat metabolism Absorption of glucose is more rapid than normal. This results in a transient hyperglycemic phase followed by hypoglycemia This latter phase may produce characteristic symptoms A high protein low carbohydrate diet is efficacious in preventing these abnormalities

Likewise there is no experimental evidence that gastrectomy will produce pernicious anemia Clinical experience also indicates that primary anemia is rarely encountered following various gastric operations However many patients do develop anemia but this is of the hypochromic microcytic type commonly associated with iron deficiency Improvement is consistently apparent with administration of hydrochloric acid with the diet or ferrous iron The hemoglobin level will remain satisfactory as long as the patient takes ferrous iron one week out of each month In most of the authors patients 0 32 Gm ferrous sulfate three times daily for one week

(5) S gery 13 823 833 Ju e 1943

quirement for manganese cobalt and zinc is so meager that the possibility of deficiency of any one of them can not be dismissed although because of their broad distribution in nature and probably small requirement the likelihood of acute or widespread deficiency appears remote The essential trace elements and the other trace elements which occur in living matter but whose importance is unknown challenge nutritionists and physiologists The indispensable traces just as the vitamins appear to be keys to fundamental physiologic processes the mechanisms of which are either only partially understood or completely unknown

Metabolic Abnormalities in Patients with Cancer of the Gastro Intestinal Tract From a review of recent studies made by Jules C Abels Irving Ariel Paul E Rekers George T Pack and C P Rhoads[4] (Memorial Hosp New York City) it is apparent that patients with gastro intestinal cancer suffer from several metabolic abnormalities which may endanger their operative and postoperative course Many of these abnormalities probably are related to hepatic insufficiency which probably is induced by the presence of the gastro intestinal neoplasm Removal of the cancer often is followed by disappearance of the metabolic dyscrasias principally that which involves the fabrication of serum protein However other dysfunctions of which hypoprothrombinemia is the most prominent persist well into the postoperative period Total and perhaps subtotal gastric resection although necessary for surgical treatment of the patient may institute a new metabolic disturbance—steatorrhea and consequent loss of weight

A proper recognition of these preoperative and postoperative complications should be necessary for the best treatment of the patient with gastro intestinal cancer While it may be impossible at present to counteract all of these abnormalities many can be corrected in time to prevent serious consequences

[The correction of electrolyte nitrogen vitamin hematologic

(4) A h S g 46 844 860 J 1943

special nutrients for moderately active men in health

The deficient diet was composed of common foods and the menus were such as might be found on the tables of about one third or more of the population of the United States The deficient diets used contained approximately 0 65 mg thiamine and 0 94 mg riboflavin about one third of the recommended daily requirement The deficient diet produced a definite decrease in work output shortly after it was begun despite the lack of physical signs of a deficiency All of the changes mentioned returned to normal or better following administration of yeast concentrate

Difficult muscular effort such as the civilian industrial or Army worker must exert with consequent greater combustion of carbohydrate should lead to a greater requirement of vitamins Use of natural foods to bring inadequate diets to the required level is the ideal solution but until this plan shall have become workable discriminate vitamin administration to the civilian or industrial worker on an inadequate diet is a sound policy

Effects of a Diet Deficient in Vitamin B Complex on Sedentary Men are described by E Egaña R E Johnson R Bloomfield L Brouha A P Meiklejohn J Whittenberger P C Darling C Heath A Graybiel and F Consolazio[7] (Harvard Univ) Seven healthy physicians between 27 and 42 years of age were placed on a vitamin B complex deficient diet adequate in calories and proteins for periods up to four weeks then brewers yeast was added to the diet for two weeks after which a normal diet was followed No time elapsed between periods and the subjects carried on their ordinary laboratory and hospital duties

Observations were made at regular intervals on the subjects at rest and during exercise In general a subject had either the same reactions as the rest of the group or none Reactions were never the reverse of those of the remainder of the group

(7) Am J Phy ! 137 731 741 Nov mber 194

each month prevented hypochromic microcytic anemia

Gastro intestinal motility is decreased rather than increased This may be due to intra abdominal section of the vagus nerves in the course of total gastrectomy

The mortality rate following total gastrectomy is not prohibitive The authors report 2 deaths in the last 19 consecutive operations One of these occurred in a man aged 79

Relationship between Vitamin B Complex Intake and Work Output in Trained Subjects was studied by Clifford J Barborka Eliot E Foltz and Andrew C Ivy[6] (Northwestern Univ) Four subjects who had been existing on a controlled adequate diet and who had been trained on the bicycle ergometer for from nine months to one year were placed on a diet deficient principally in vitamin B complex During the 82 days on this diet the subjects developed irritability easy fatigability lack of pep anorexia and increased leg pain during the work periods but at no time did they develop any objective physical signs of vitamin B complex deficiency The 24 hour urinary excretion of thiamine and riboflavin dropped to low levels The blood thiamine remained in the normal range The blood pyruvic acid following exhaustion was likewise unaffected However as the deficiency progressed the milligrams of pyruvic acid in the blood per calorie of work done increased more than 50 per cent This ratio may prove to be a useful indicator of fairly early vitamin B complex deficiency

The recommended daily allowances for the various dietary essentials (prescribed by the Food and Nutrition Board of the National Research Council) were set up to serve as a guide for planning adequate nutrition for the civilian population of the United States The authors used therefore in their adequately controlled diets (during the training period and establishment of the plateau level of work output) 1 8 mg thiamine and 2 7 mg riboflavin which is the recommended daily amount of these

(6) J A M A 1 71 0 Jul 10 1943

William Sawyer Eisenstadt[8] (Minneapolis) reports two cases of hypersensitivity and analyzes their similarities Both patients showed allergic reactions to thiamine hydrochloride given parenterally but subsequently tolerated it when given orally It may be that these patients had a high threshold of sensitivity to vitamin B_1 and that oral administration did not maintain the thiamine hydrochloride concentration at a sufficiently high level to evoke an allergic reaction the situation is analogous for the normal daily dietary intake of vitamin B_1

Normally the latent period for production of sensitization does not exceed 7 10 days As long as thiamine hydrochloride was injected at an interval of less than seven days no reaction resulted but when the interval exceeded one week both patients had an anaphylactic reaction In both cases intradermal tests were positive and passive transfer tests negative Absence of demonstrable circulating antibodies does not preclude clinical sensitivity however serum of low antibody titer may be present

With the establishment of the possibility of thiamine hydrochloride sensitivity skin testing of patients about to receive the drug parenterally may be a wise measure especially if it has been given previously

Excretion of Thiamine Riboflavin Niacin and Pantothenic Acid in Human Sweat Theodore Cornbleet Ernst R Kirch and Olaf Bergeim[9] (Univ of Illinois) found heat sweat to contain an average of 150 μg thiamine 120 μg riboflavin 300 μg pantothenic acid and 200 μg nicotinic acid per L These values correspond for thiamine to about 5 per cent of intake on a good diet for riboflavin and pantothenic acid to about 3 per cent and for nicotinic acid to about 0 5 per cent For average American diets the percentages would be more nearly 10 per cent for thiamine 5 per cent for riboflavin and 1 per cent for nicotinic acid The excretion of such amounts of these vitamins cannot be said to be negligible from

(8) Mi n sota M d 25 861-863 Novemb 1942
(9) J A M A 12 426-429 J e 12 1943

Analysis of daily thiamine output and excretion rate of test doses revealed deficiency within four weeks Symptoms of deficiency were mild and vague the most outstanding being easy fatigue loss of ambition and loss of efficiency in daily work Moderate deterioration in physical fitness for exhausting exercise and poor recuperation between bouts were regular findings All symptoms disappeared when brewers' yeast was added to the diet

Measurements of oxygen consumption carbon dioxide excretion, blood lactate blood pyruvate blood sugar, urine lactate and urine pyruvate showed either slight abnormal changes or none during rest and moderate and exhausting exercise and after exhausting exercise Cardiovascular changes were inconstant There was no tachycardia on exertion During moderate and exhausting exercise heart rates tended to be abnormally slow Blood pressure showed no abnormal changes Electrocardiography revealed significant changes in only one patient

Under these experimental conditions only the amounts of vitamins found in the urine and symptoms and signs suggesting deterioration of the efficiency of the whole organism can be relied on to detect early deficiency Symptoms and signs that clear on administration of brewers yeast in adequate amounts are likely due to previous vitamin B complex deficiency

Moderate deterioration in sedentary subjects differs from that in manual laborers with vitamin B complex deficiency The latter complain of acute symptoms and serious impairment of fitness for work within five days

Hypersensitivity to Thiamine Hydrochloride Parenteral administrations of thiamine hydrochloride have caused both toxic and allergic reactions Those listed in the literature include throat constriction, epigastric fulness nausea vomiting herpes zoster following intensive therapy, violent sneezing edema of the lips and eyelids tightness in the chest increased pulse rate, excessive nervousness and profuse perspiration In one case death followed an anaphylactic reaction

spond favorably to the administration of this vitamin

Of the 20 patients studied 3 had more than one of these lesions One of these had cheilosis a magenta colored tongue with enlarged papillae corneal opacities and conjunctival injection The other two had both cheilosis and the magenta colored tongue with flattened papillae Nine of the 20 subjects had ocular lesions with both subjective and objective manifestations 5 of the total group had cheilosis 6 had glossitis and 4 had pemphigus vulgaris

Synthetic riboflavin was administered orally Dosage during the first week or two was 6 mg daily in divided doses In the absence of response the amount was increased Achlorhydric patients received in addition at least 1 cc dilute hydrochloric acid with each meal If no favorable response occurred after combined therapy riboflavin was discontinued and another vitamin prescribed Patients with ocular lesions also received such local therapy as atropine and heat

No significantly favorable response was observed in any of these cases Of the five patients with cheilosis none responded to riboflavin three of these also received no benefit from vitamin B_6 but all finally responded to brewers yeast No improvement was noted in the four patients with pemphigus three of these died while under observation Of the nine patients with corneal lesions five at first showed temporary subjective and objective improvement but relapsed while riboflavin therapy was continued One experienced permanent subjective improvement without however any objective change In none of the six patients with glossitis was the appearance of the tongue significantly altered by riboflavin therapy a return to normal occurred in four after brewers yeast and in one after pyridoxine was administered

Conditioned Malnutrition The term malnutrition signifies not a dietary inadequacy but a tissue deficiency of an essential nutrient Norman Jolliffe[3] (New

(3) J A M A 122 99 306 May 29 1943

the physiologic standpoint although it becomes of real importance perhaps only in case of profuse sweating or *when the diet is low in these vitamins Elimination of* nicotinic acid could hardly be of importance in any case The losses of the other vitamins are of the same order as losses reported for ascorbic acid in sweat Since favorable results have been reported with administration of ascorbic acid in cases of profuse perspiration it is possible that supplements of other vitamins might be worthy of trial under similar conditions Ingestion or intramuscular injection of large amounts of these vitamins did not lead to any noticeable or persistent increase of their secretion in the sweat

These vitamins as found in sweat appear to be a true excretion not appreciably influenced by bacteria on the skin Sweat contains sufficient of the vitamins to promote bacterial growth provided conditions are otherwise favorable Thiamine appears to exist in sweat only in the free form

Studies of B Vitamins in the Human Subject Failure of Riboflavin Therapy in Patients with Accepted Picture of Riboflavin Deficiency Conflicting data in the literature and experience with 20 cases of so called ariboflavinosis with lesions of the lips cornea and tongue usually ascribed to riboflavin deficiency have caused Thomas E Machella and P Robb McDonald[2] (Univ of Pennsylvania) to doubt the validity of this syndrome Clinical phenomena attributed to riboflavin deficiency are (1) cheilosis (2) seborrheic dermatitis found in the nasolabial folds on the alae nasi in the nasal vestibule and on the ears (3) a vascularizing keratitis manifested by dimness of vision photophobia lacrimation and burning and on slit lamp examination by corneal vascularization (4) a specific form of glossitis characterized by a purple red or magenta color of the tongue and *by enlargement or flattening of its filiform* papillae Pemphigus vulgaris though not attributed to riboflavin deficiency has been reported to re

(2) Am J M Sc 205 214 [illegible]

ficiency is diagnosed Secondary pellagra is associated with alimentary tract disease infections (pneumonia and tuberculosis) heart disease surgical conditions and cirrhosis

Diagnosis and treatment of secondary deficiency diseases may determine the outcome of primary diseases

Experiences in Salt Deficiency J M Flattery (R A N) states that salt deficiency gives rise to sickness of varying intensity and in some instances may prove fatal Such deficiency usually occurs under conditions which give rise to excessive sweating When such conditions exist therefore salt loss must always be considered in the diagnosis of any case associated with abdominal symptoms Administration of salt is attended by almost immediate response A successful prophylactic measure consists of taking ½ teaspoon of salt in water twice daily This should be instituted for men on all ships serving in the tropics for those on ships during passage through tropical areas (especially troopships) and also for all personnel living and stationed ashore in tropical areas

Maintenance of Nitrogen Equilibrium by Intravenous Administration of Amino Acids Clinical studies by Samuel S Altshuler Hilda M Hensel Paul Hecht and Richard Pursley[6] (Eloise Mich) were based on previous observations that substitution of a mixture of essential amino acids for food protein is possible A hydrolysate of casein re enforced by tryptophan was given subcutaneously or intravenously to normal persons and to patients after operation Five of seven normal subjects stayed on nitrogen balance throughout the experiment In the surgical patients the injections helped to maintain nitrogen equilibrium

In the present study it was observed that solutions of amino-acids administered intravenously to 19 patients with various diseases were uniformly well tolerated Over 94 per cent of the amino acids given by this route was

(5) M J A tr l 1 5 7 J " 1943
(6) A h Int M d 70 749 762 N mbe 1942

York City) states that this tissue deficiency may be caused by failure to ingest an adequate diet, by factors which interfere with ingestion absorption or utilization of essential nutrients or by factors which increase the requirements for vitamins, their destruction or excretion These are known as conditioning factors and when a deficiency disease is produced through their mediation it is known as a conditioned deficiency disease or conditioned malnutrition The more common illnesses, physiologic factors and therapeutic measures that may produce a conditioned deficiency disease are listed and briefly discussed From this it is evident that many diseases and some of the therapeutic measures used to combat them interfere with nutrition and are potent factors in production of deficiency diseases Treatment of malnutrition is in each person an individual medical problem requiring exact diagnosis and therapeutic measures

Deficiency Diseases are discussed by M A Blankenhorn[4] From June 1938, to January 1942 210 patients with one or more deficiency diseases were found among 9,530 medical admissions to the Cincinnati General Hospital After subtracting the 14 with multiple deficiencies, a case incidence of deficiency diseases of 2 per cent remains of which 1 per cent was liver cirrhosis Other diseases were in order of frequency nutritional neuritis niacin deficiency pellagra and riboflavin deficiency Scurvy beriberi heart disease and clinical vitamin A deficiency were rare Deficiency diseases occurred most frequently in association with other diseases chiefly those interfering with eating or diet selection

Diagnosis is difficult from the patient's history alone Few of the urine and blood tests are of value Consequently, the physician must resort to careful examination and trial by treatment

Pellagra is diagnosed when symptoms present are glossitis, enteritis dermatitis dementia neuritis due to lack of vitamin B_1 sore lips and ophthalmia caused by lack of riboflavin In cases of glossitis alone niacine de

(4) Ohio State M J 38 1005 1010 November 1942

or the outgo has diminished Von Bergman s suggestion that the fat cells of obese persons possess an abnormally great avidity for fat and an exaggerated capacity for retaining it finds no support in experiments designed to test its validity With regard to hereditary factors it is stated that body build is inherited obesity is not

Disproportion between energy inflow and outflow is brought about by an abnormality of the appetite Exces sive eating is an expression of a mood While no attempt is made to discuss the ultimate origins of behavior the understanding of obesity will be advanced by listing proximate causes to which some persons respond (in part) by overeating (1) overemphasis by a parent of the importance of food in a child s upbringing (2) grat ification obtained from the flavors of foods (3) the feel ing of repose and comfort produced by a full stomach (4) the temporary respite from anguish caused by in tellectual social or sexual failure (5) the food habits of youth which are carried over into middle age even though the need for food is diminished and (6) disabling disease with its lessened energy requirement which is compensated for by indulgence in food

Weight can always be reduced by adherence to a re stricted diet but co operation by the patient is unlikely until the nature of obesity is elucidated and his particu lar reason for overeating has been discovered and ex plained to him The chronicity of his ailment and its lack of immediately disabling features and of severe pain make it easy to find excuses for delaying treatment and for being lax about it Most patients are unaware of the threat to life that obesity entails and they can scarcely be expected to take their condition seriously until they acquire the information

Effect of a High Fat Test Meal on Blood Cholesterol in Normal and Obese Individuals Elliot Oppenheim and Maurice Bruger[8] (Columbia Univ) report that in subjects with normal body weight ingestion of a diet low in fat and cholesterol or a test meal high in fat (500 cc

(8) Am J M S 205 77-8 J ry 1943

utilized in nine patients with malignant neoplasms three with hyperthyroidism one patient with hypothyroidism, two patients with chronic infections two with chronic nephritis and two with cirrhosis of the liver These observations indicate that solutions of amino acids can be administered intravenously at the rate of 1 to 2 Gm amino acid nitrogen per hour

[There are numerous indications in both medical and surgical fields for this form of therapy With modifications and refinements have come better utilization and less unfavorable reactions Aside from its availability its low cost in comparison to blood or plasma has much to recommend it —Ed]

Obesity L H Newburgh[7] (Ann Arbor Mich) presents a comprehensive study of obesity Many investigations of the metabolism of obese persons have failed to disclose any abnormal process that accounts for the fat accumulation On the contrary they have demonstrated that obese persons produce more heat in the basal state that they expend more energy to perform a measured amount of work and that their total heat production is greater than that of normal persons of similar age height and sex under the same circumstances Since they are unable to absorb more energy from their food, they must eat more than normal people simply to avoid loss of weight

A review of the relation of endocrine disorders to obesity indicates that obesity is never directly produced by increased or diminished activity of an endocrine gland *In other words no internal secretion is capable* of so changing the metabolism that the total amount of fat in the body will increase unless the inflow of calories is greater than the outflow It remains for the future to decide whether a hypothalamic disorder or other cerebral disease is capable of causing human obesity through abnormal stimulation of the appetite Whatever the answer the simple principle will remain that obesity is invariably the result of a disproportion between energy inflow and outflow The former must always be greater than the latter because either the intake has increased

(7) *Arch Int M d* 70 1033 1096 Decemb r 1942

Food allergy as a cause of bronchial asthma nasal allergy migraine recurrent headache cyclic vomiting of childhood various gastro intestinal symptoms urticaria angioneurotic edema and atopic dermatitis is pointed out The possible role of food allergy in acne vulgaris chronic ulcerative colitis allergic arthropathies and urogenital and cardiovascular manifestations is also considered

Some Clinical Observations in Cases of Anorexia Nervosa J M Berkman presents observations on two cases which together with other experiences led him to conclude that desiccated thyroid is rarely indicated in anorexia nervosa

Girl, 16 was first seen in August 1941 In February 1940 she lost her appetite and within several months her weight which had been 130 lb had dropped to 83 lb Examination disclosed marked dryness of the skin and hair blood pressure 82/60 pulse 48 temperature 97 2 F weight 78 lb and height 5 ft 7 in Except for the marked weight loss and a small atrophic uterus physical examination was essentially negative Laboratory data were either negative or within normal limits except for a concentration of 69 mg of sugar per 100 cc blood and two basal metabolic rates of —37 and —34 per cent

The patient was encouraged to follow a diet which included a gradually increasing number of calories With considerable effort 6 lb was gained during the initial three week observation period She was also given 2 gr desiccated thyroid daily and after seven days of such therapy the basal metabolic rate was —26 per cent She was given dietary instructions advised to continue thyroid therapy and dismissed

Three months later the basal metabolic rate was —40 and —38 per cent on two occasions Her weight was 80 lb Thyroid which presumably through lack of absorption had not had any effect was discontinued Again she gained only 6 lb

The patient returned on Aug 25 1942 Her weight was 128 lb She had a good appetite and for two or three months had had no difficulty in eating or discomfort or sensation of fulness after eating Intolerance to cold had not been noticeable Personality changes were likewise marked Blood sugar concentration was 73 mg per 100 cc blood and the basal metabolic rate on two occasions was —26 and —27 per cent respectively These basal metabolic rates were considered to indicate a significant increase in heat production With con

( ) P St ff M et M y Cl 18 81 86 M 4 1943

Chicago) report observations made over a year on 152 boarding school children aged 2–14 whose diet was supplemented with all foods necessary to bring it up to the standard dietary pattern Supplementary foods included (1) 1 pt more of milk daily (2) 5 eggs per week (3) 1 oz cheese three times a week (4) 1 oz butter daily (5) whole grain cereal each morning (6) pineapple juice ad libitum and (7) 5 oz ice cream twice weekly

Daily records of the amounts of foods consumed showed acceptance of the supplementary foods in adequate amounts in 94–99 per cent of all the times they were offered Analysis of the childrens diets before fortifying showed that they were below the standards for all factors except vitamin A There was an average deficiency of 30 per cent in calories 20 per cent in protein 31 per cent in calcium 17 per cent in riboflavin 51 per cent in thiamine and 43 per cent in vitamin C Some of the greatest deficiencies were found in the diets of the 13–15 year age group After supplementation weighing and assay of the diets actually consumed showed that the intake of all food factors equaled or exceeded the recommended allowances Caloric content however remained slightly below optimal figures

The authors conclude from this portion of the study that children can and will eat basic foods in adequate amounts if offered under conditions favorable to their acceptance

Growth in Weight and Height—Ruth Blair Lydia J Roberts and Marjorie Greider[3] (Univ of Chicago) found that the dietary supplementation had a beneficial effect on growth of the children as shown by gains greater than expected according to Baldwin Wood tables Before fortification of the diet the group averaged 61 per cent of its expected gain in weight for the supplementary period the figure was 140 per cent The number of children below average height decreased significantly and in most individuals there was a closer

(3) J P d t. 27 410 417 N mber 1945

approximation to the ideal height weight ratio Children who received the fortified diet more regularly and for longer periods made better gains than did others

The authors believe that these effects on height and weight demonstrate that the children s diets were originally inadequate In only a few cases did the increase in weight on the fortified diet represent accumulation of fat beyond what was needed or desirable

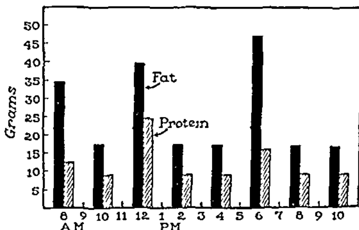
Blood and Urinary Excretion Studies before and after Dietary Improvement —Helen Oldham Lydia J Roberts and Marjorie Young[4] (Univ of Chicago) determined vitamin C levels in all children and serum protein vitamin A carotene hemoglobin and thiamine values in 39 in over 30 children excretion studies of thiamine and riboflavin were performed Levels of vitamin C and B_1 were significantly below normal on the regular institutional diet Supplementing the diet produced significant improvement as measured by estimations of the blood levels test dose returns and one hour fasting excretions

Total Solids, Fat and Nitrogen in Feces—*Study of Normal Persons and of Patients with Duodenal Ulcer on a Test Diet Containing Large Amounts of Fat* —Eric E Wollaeger Mandred W Comfort James F Weir and Arnold E Osterberg[5] (Mayo Clinic) measured the total solids fat (all ether soluble substances or total lipoids) and nitrogen in the feces of six healthy adults and of seven patients with duodenal ulcers all of whom were given the identical test diet high in fat (Fig 144) Since the results in the two groups showed no significant difference they were combined into a single control series for comparison with results of similar studies on patients who had undergone various gastric operations

Despite the completely uniform dietary intake the fecal components studied varied considerably The total fecal solids varied from 15 5 to 40 4 Gm per day with an average of 26 6 Gm the fecal fat from 5 5 to 13 6 Gm per day with an average of 8 7 Gm These figures

(4) J P d t 27 418 4 7 Nov mbe 1945
(5) G t t l gy 6 83 9 F b y 1946

demonstrate again the great ability of a normal subject to utilize large amounts of dietary fat The fecal nitrogen varied from 0 6 to 1 9 Gm per day with an average of 1 2 Gm these values lie within the usual normal range Determination of the percentage of the total fecal



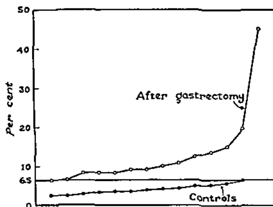
Fg 144—D t b t f f t d p ot n d ly m nu f test d et (C u t sy f W ll g E c E C mfo t Ma d ed W W J m F d O t be g A n ld E G t o t logy 6 83 9 F br y 1946)

solids which is represented by fat without regard for the amount of fat ingested would not be a satisfactory test for steatorrhea

Study of Persons Who Had Undergone Partial Gastrectomy with Anastomosis of Entire Cut End of Stomach to Jejunum (Polya Anastomosis)—Wollaeger Comfort Weir and Osterberg[6] by means of intake-excretion studies determined the total solids fat and nitrogen in the feces of 14 patients who had undergone partial gastrectomy with anastomosis of the entire cut end of the stomach to the jejunum The high fat test diet used in the earlier study was given to 10 patients and diets containing half as much fat were given to the other 4 Nearly all the persons who were operated on lost more fat

(6) G troe ter logy 6 93 104 F b y 1946

in the stool when taking a high fat diet than did those who had not undergone an operation on the stomach (Fig 145) This loss occurred in patients who did not complain of symptoms referable to their digestive tracts but it tended to be greater among patients with post operative digestive complaints (not associated with re curring peptic ulceration) Excessive loss of fat in the



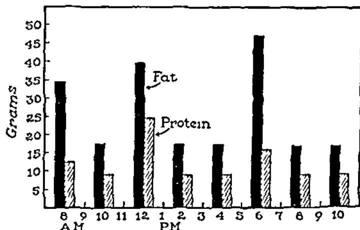
Fg 145—P t g f ng ted f t l t n t l f 27 bj t (g d d of d g f f t l) P t g d t d by t sk p ent h gh t l p d by l d gnat d p t t y p d f t dy (Court y f W ll g E D C mf t M d ed W W J m F d O terb g A n ld E G t oe t logy 6 93 104 F b ry 1946)

feces was also observed in the few patients who received diets of ordinary fat content Some of the patients who were operated on lost more nitrogen and total solids in the stool than did those who had not undergone an operation on the stomach The excessive amounts of fat and nitrogen in the feces were not large in most in stances but unless the patient should take a diet of suf ficient caloric content to compensate for the loss a de crease in body weight might be expected

[Three forms of sequelae of partial gastrectomy for chronic peptic ulcer duodenal ulcer in particular are anastomotic ulcer postoperative gastritis and malnutrition of variable degree The last mentioned disorder may prove very refractory so that the patient does not regain his former weight A desire to determine

demonstrate again the great ability of a normal subject to utilize large amounts of dietary fat The fecal nitrogen varied from 0 6 to 1 9 Gm per day with an average of 1 2 Gm these values lie within the usual normal range

Determination of the percentage of the total fecal



F g 144—D t b t n f f t d p t d ly m nu of t st d t (Co t y f W lla g E E C mf rt M 1 1 W W J m F a 1 Ost r be g Arnold E G st oenter l gy 6 83 9 F b u y 1946)

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(6) G troe t ology 6 93 104 F bru y 1946

by the modified Sulkowitch test is increased in any disease with rapid general skeletal decalcification Highest values are usually found in hyperparathyroidism and

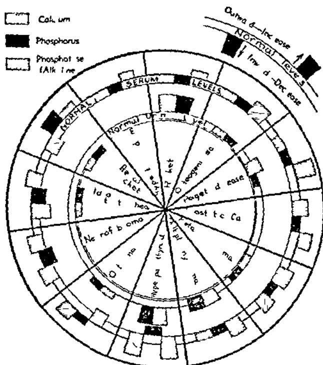


Fig 146—Cl n cal wh l f cal m d ph phoru d st b ces sch mat p se tat of d ff e t l diag o t f tu f alt ed calc m f ph phoru met bol m, T ad wh el g P g t d sease—increased lkal ne phosphatase no mal calcium nd ph phoru f serum n rmal na y phosphoru h t l ed calc m (Co rtes f E s G T d Fl k E B Mod rn Med. 13 63 76 No embe 1945)

hyperthyroidism Occasionally a hidden hyperparathyroidism may be demonstrated in a patient with urinary calculi by the finding of increased urinary calcium on the Sulkowitch tes When normal phosphatase hypercalcemia and hyperglobulinemia are found on laboratory

the obscure underlying cause or causes for this condition and possible means of correction was the incentive for this timely and highly desirable investigation —Ed]

Calcium, Phosphorus, Phosphatase Diagnostic Implications G T Evans and E B Flink[7] (Univ of Minnesota) review laboratory findings in disorders of calcium phosphorus and phosphatase metabolism and present differential diagnostic features of the diseases in which these occur (see Table) Most bone diseases may

DIFFERENTIAL DIAGNOSTIC FEATURES OF DISEASES WITH DISTURBED CALCIUM AND PHOSPHORUS METABOLISM*

	S um			U		F
C o	C	P	Pt (Alk l)	C	P	Ca
Hype p tl y l	I	D	N to I	I	I	N
Hyperthy l	N	N	N to I	I	I	I
I g t l	N	N	I	N to I	N	
M lt l y l m	N to I	N	N	N to I	N to I	
Rickets	N	D to N	I	D	D	
O te l	D to N	D	I	D	D	D
Il j tl ste to lea	D to N	D to N	N to I	D	D	I
J l k t	D to N	I	I	D	D	
O t og m	N	N	N to I	N	N	
M ta t t c c e n	N to I	N	N to I	I	I	
I t t m	N to I	N	I			
N i fl o t	N to I	D to N	N to I			
U	D	I	N	D	D	
R g g t l j l			I			
Hy l l m †	I	N				
Hypo t e at	D	N				
A l ‡	N	N				
Alk l ‡	N	N				
Hy t tly l m§	D	I	N	D	D	
H gl t D tl p	I	I	N	I	I	

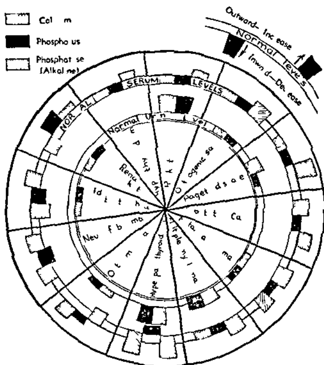
N l te l D d c d I c a l.
† C l m f t n m l
‡ C l f t d t b d
§ Re l f t m l

be recognized by clinical and roentgenographic study but there are cases in which diagnosis cannot be made without laboratory examination

The level of alkaline phosphatase depends chiefly on the amount of osteoblastic activity (in the nonjaundiced subject) Increase in alkaline phosphatase is not pathognomonic of any one pathologic condition being found in rickets hyperparathyroidism Paget s disease neoplasms of the bone etc Elevation of acid phosphatase however is fairly specific for bone metastasis of prostatic carcinoma Urinary calcium excretion as measured

(7) Mod n Med. 13 63 76 N mb 1945

by the modified Sulkowitch test is increased in any disease with rapid general skeletal decalcification Highest values are usually found in hyperparathyroidism and



F g 146 —Cl l wh l f al m d pl ph s d t b ce h m t p esentat n f d ff l d g t f t s f lte ed lc m d ph ph ru m tabol m T d wh l g Paget a d s ase— sed lk l pho ph t m l l m a d phosph ru f serum orm l ry ph phoru L t l t d ry c l m (C te y f E G T a d Fl nk E. B Mod Med 13 63 76 N mber 1945)

hyperthyroidism Occasionally a hidden hyperparathyroidism may be demonstrated in a patient with urinary calculi by the finding of increased urinary calcium on the Sulkowitch test When normal phosphatase hypercalcemia and hyperglobulinemia are found on laboratory

examination diagnosis of multiple myeloma should be considered In hypocalcemic tetany rapid and simple confirmation of diagnosis can be made by use of the qualitative Sulkowitch test Absence of precipitate usually means a serum calcium (with normal protein) of 8 mg or less per 100 cc Differentiation of renal rickets with its secondary parathyroid hyperplasia from primary hyperplasia may be difficult by laboratory examination and occasionally requires microscopic study of the excised gland

Effect of Folic Acid on Sprue Tom D Spies Guillermo Garcia Lopez Jose Aristides Menendez Virginia Minnich and Mary B Koch[8] (Univ of Cincinnati) report results of treatment in three carefully selected cases which met the following criteria a macrocytic anemia erythrocyte counts of 2 00 000 or below a color index over 1 megaloblasts and the typical erythroblastic arrest in the bone marrow fatty stools weight loss and no recent treatment or complicating disease The patients were hospitalized and their diets restricted to fruits vegetables cereals bread butter lard sugar and coffee Meat meat products fish and poultry were excluded After a control period each patient was given 200 mg folic acid by mouth daily in two divided doses On the third and fourth days of treatment increase in appetite and strength was noted Reticulocytes increased strikingly on the fourth and fifth days and reached a maximum by the sixth or seventh day after folic acid administration was started There was a corresponding rise in hemoglobin and erythrocyte count Though strength vigor and appetite improved markedly diarrhea did not entirely disappear during the observation period There were recurrences of watery foul stools during the period of blood regeneration

[Subsequent reports by other observers confirm the efficacy of folic acid in the treatment not only of sprue but of macrocytic hyperchromic anemias in general the most prominent of which is pernicious anemia —Ed]

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(8) South M J 39 30 3 Jan y 1946

Retention of Electrolyte during Recovery from Severe Dehydration Due to Diarrhea The general plan of Daniel C Darrow's[9] (Yale Univ) experiments was to obtain the actual retentions of the chief extra and intracellular ions of six infants during recovery from dehydration of diarrhea Normal food intake and weight gain for two or more days were the criteria for recovery These requirements were met in all but two patients and even they were gaining weight two days after the end of the study

Blood was taken under mineral oil and the baby placed on a metabolism bed Urine was preserved with thymol or toluol Stool collections were demarcated at the end of each period by giving a little carmine orally Blood samples were taken at the end of each period Nothing was given by mouth during the first period A slow intravenous drip of solutions containing sodium chloride sodium lactate and glucose was given to four patients In addition two patients were given potassium chloride to permit a comparison of the effects of conventional therapy with the new type that from the beginning uses potassium salts parenterally It was found that babies look better than after the usual treatment and recover from ordinarily fatal diarrheal attacks

Blood and plasma were given when indicated During the second period food was given at submaintenance levels Potassium chloride (1–2 Gm) was added to the food with one exception The basic food was powdered whole milk mixed with powdered skimmed milk The mixture had about 2 per cent fat and 3 5 per cent protein Dextrimaltose equal to 10 per cent of the mixture was added It was free from salt in five cases The food was mixed with water to insure adequate fluid intake

Diarrhea led to a decrease in extracellular water owing to loss of sodium and chloride in extracellular fluid Loss of extracellular sodium is explainable in some cases by the transfer of sodium from extra to intracellular fluids This would explain the acidosis of one patient In other

(9) J P d t 28 515 540 M y 1946

cases sodium was lost from intra and extracellular fluids Because of the tendency to retain sodium chloride it was hard to determine the extent of the deficits of extracellular sodium and chloride on admission Moderate overexpansion of extracellular fluids is undoubtedly less harmful than under replacement of sodium and chloride

Lost nitrogen was rapidly restored as soon as food was taken However data do not show the extent of the deficit before the patients entered the hospital

In all cases there was loss of intracellular potassium and in two babies it was about one fourth of the estimated normal potassium content The safe dose of potassium for intravenous or subcutaneous use is predictable If the concentration of serum potassium is 5 mm per L a rise in concentration of 4 5 mm will not produce heart block Assuming equal distribution throughout body water 3 1 mm potassium per kg body weight will produce a rise of 4 5 mm in the concentration of serum potassium Injected slowly over a period of four to eight hours this should be safe unless the serum concentration is already high and urine is not being formed

For a solution for parenteral use the concentrations used in this study were potassium chloride 40 sodium chloride 100 and sodium lactate 50 mm per L This solution can be made by adding 40 cc molar sodium lactate 2 Gm potassium chloride and 3 Gm sodium chloride to 710 cc water The sodium chloride and potassium chloride can be sterilized separately and added together with one 40 cc ampule of molar sodium lactate to 710 cc sterile water This is given subcutaneously and will not produce potassium intoxication in the recommended doses given for four to eight hours

Perhaps in all cases of severe diarrhea infusions of physiologic saline and glucose solutions should be given for an hour or until urine formation is evident Then the solution containing potassium chloride can be started

Decrease in muscle phosphorus of dying infants has been shown *to equal about 10 per cent of the normal*

content It does not seem as yet that a phosphorus deficit is of great importance in diarrhea

[The author s reference to the loss of potassium is of interest because it is well known that a deficiency of serum potassium results in paralysis of the voluntary muscles Such deficiency is present in familiar periodic paralysi and may occur in chronic nephritis According to Holler (*Journal of the Am rican Medical Association* 131 1186 1189 Aug 10 1946) it may occur during treatment of diabetic acidosi Such a complication could easily prove fatal if not recognized in time and promptly treated —Ed]

Paralytic Ileus in Severe Hypothyroidism P A Bastenie[1] (Univ of Brussels) finds that the importance and



Fg 147 (C t y f E t P A La t 1 413 416 M 23 1946)

severity of the intestinal signs and symptoms in myxedema have not been sufficiently emphasized Ballooning of the abdomen by flatulent distention of the intestines may be important diagnostically in patients with unrecognized hypothyroidism in whom other signs are minimal (Fig 147) Megacolon may develop in the course of severe thyroid deficiency and may give rise to true paralytic ileus the exact etiology of which should be recognized if disastrous surgical intervention is to be avoided

In Bastenie s series of 29 patients with myxedema 19 showed significant intestinal signs i e persistent constipation intestinal distention tympanism and considerable increase in tension of the abdominal wall 3 in whom the condition was severe had partial obstruction

(1) L t 1 413 416 M 23 1946

In four cases of severe hypothyroidism secondary to destruction of the pituitary there was one case of severe intestinal paresis

Intestinal paresis in hypothyroidism may be chronic or acute Chronic paresis is found in hypothyroidism of long duration and the clinical picture is characterized by increasingly severe constipation and progressive distention of the abdomen which may be as marked as it is in peritonitis or intestinal obstruction Roentgenography *shows gross flatulent distention of the intestine* sometimes with loculi or fluid No organic obstruction is found although there is often dolichomegacolon In other cases the abdomen enlarges so rapidly that a cyst or tumor is suspected Paralytic ileus may be acute and alarming Autopsy usually reveals enormous distention and elongation of the colon in one case it was 330 cm long The wall of the colon is thickened and has lost its elasticity Microscopy reveals myxedematous infiltration of the stroma atrophy of the mucosa diffuse infiltration of the submucosa by lymphocytes and plasma cells and diminution of glandular crypts Apparently deposition of myxedematous material separating the muscular *fibers from the ganglions of Auerbach's plexus explains* the loss of elasticity and the intestinal paralysis Treatment is that of myxedema

It seems practical to speak of an intestinal form of acquired myxedema in adults and to include in the differential diagnosis of intestinal obstruction the paralytic ileus of myxedema

[Unexplainable constipation in an adult previously having normal bowel function should lead to the suspicion of the presence of hypothyroidism (myxedema) The more marked intestinal disturbances cited by the author are illuminating Severe chronic cases of *myxedema may also give rise to a cites* One such case came under our observation recently The response to intensive substitution therapy was slow but eventually very satisfactory —Ed]

Malnutrition is discussed by Helmuth Sprinz (M C A U S) *The emphasis on the importance of various* nutrients has now been shifted from vitamins to pro

( ) M Cl n No th Am ca 30 363 384 M r h 1946

teins Of all the factors influencing the amount of protein metabolized the most outstanding is the increased de mand due to illness or injury The loss of protein during disease is spoken of as toxic destruction of protein Protein deficiency is a common and serious complica tion in numerous medical and surgical conditions Symp toms of protein deficiency are mental depression which may progress to apathy confusion and incontinence of urine and feces There are lack of appetite weakness and lassitude Protein deficiency is commonly associated with weight los Nutritional edema which is one of the last phenomena of advanced protein deficiency may be absent even in fatal cases Malnourished patients are particularly susceptible to infection which is often ful minating

Sprinz relates his experiences with cases of serious malnutrition in soldiers who were chronically ill after battle trauma and resultant infection Depletion up to one half of the previou body weight has been noted

Surprisingly large amounts of protein are necessary to restore the loss of body protein The ordinary hospital diet contains insufficient protein to compensate for any significant loss there is need for supplementary protein feeding (hyperalimentation) Sprinz obtained best re sults in most cases with 0 4–0 6 Gm protein nitrogen per kg body weight daily This corresponds to a total protein intake for an average sized male of 150–250 Gm daily

In acute cases where hypoproteinemia is caused by surgical shock burn or hemorrhage the best protein replacement therapy is blood and plasma in chronic cases parenteral administration of protein hydrolysates (amigen parenamine Baxter protein hydrolysate solu tion) or a solution of pure amino acids Protein hydrol ysates and concentrated processed proteins can also be administered orally

Proper treatment of malnutrition will hasten convales cence diminish complications and save lives It can be successfully achieved even in the mo t stubborn cases

In four cases of severe hypothyroidism secondary to destruction of the pituitary there was one case of severe intestinal paresis

Intestinal paresis in hypothyroidism may be chronic or acute Chronic paresis is found in hypothyroidism of long duration and the clinical picture is characterized by increasingly severe constipation and progressive distention of the abdomen which may be as marked as it is in peritonitis or intestinal obstruction Roentgenography shows gross flatulent distention of the intestine sometimes with loculi or fluid No organic obstruction is found although there is often dolichomegacolon In other cases the abdomen enlarges so rapidly that a cyst or tumor is suspected Paralytic ileus may be acute and alarming Autopsy usually reveals enormous distention and elongation of the colon in one case it was 330 cm long The wall of the colon is thickened and has lost its elasticity Microscopy reveals myxedematous infiltration *of the stroma atrophy of the mucosa diffuse infiltra*tion of the submucosa by lymphocytes and plasma cells and diminution of glandular crypts Apparently deposition of myxedematous material separating the muscular fibers from the ganglions of Auerbach s plexus explains the loss of elasticity and the intestinal paralysis Treatment is that of myxedema

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Malnutrition is discussed by Helmuth Sprinz (M C A U S) The emphasis on the importance of various nutrients has now been shifted from vitamins to pro

( ) M Cl N th Ame ca 30 363 384 M h 1946

usually protracted illness is necessary for the occurrence of these changes but no correlation between duration of the illness and reduction of total bases can be demon

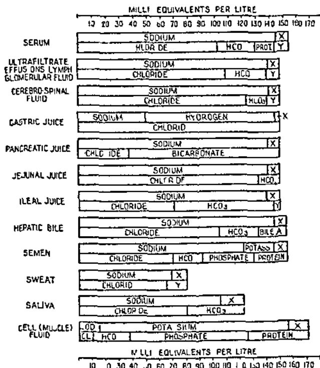


Fig 148—El t lyt tent om body fl d (ft M C R A L t 1 704 M 8 1936) d y th t d l (C t y f B b Ol J cob Act m d S d pp 160 pp 1 18 1945)

strated The mechanism producing the hyponatremia is not an abnormal loss or an insufficient supply of sodium it seems to be a rearrangement of the electrolyte regulation effected by resorption of electrolytes in the renal tubules This rearrangement proceeds gradually through excretion of electrolytes from both the extracel

Studies on Regulations of Serum Electrolytes with Survey of Water and Salt Metabolism in Organism, are reported by Ole Jacob Broch[3] (Oslo) Body fluid occurs in two main forms with essentially different compositions—cell water and extracellular fluid (Fig 148) In many pathologic conditions the organism may lose more water and electrolytes than it receives Generally the water and salt lost will be of the same composition as the body fluids The various forms of extracellular fluid have the same osmolar concentration but the concentration of electrolytes varies somewhat hence the consequences of an increased loss of fluid depend to some extent on the source of the loss Reduction of the stomach contents with their surplus supply of chloride will give rise to alkalosis whereas loss of the alkaline intestinal secretion leads to acidosis Every important loss of body fluid will produce a state of desiccation if the lost salt and water are not replaced The plasma volume is reduced and therefore hemoconcentration occurs Such dehydration may produce the most serious symptoms and even lead to death The clinical picture is in some degree characteristic and accordingly a special salt deficiency or dehydration syndrome has been established Dehydration often leads to osmolar hypotension in body fluids The salt deficiency syndrome is frequently encountered in clinical practice It is generally agreed that reduction of plasma volume is the most important factor in the pathogenesis

In most cases of febrile diseases changes sometimes of considerable extent occur in the electrolytes especially reduction of total bases and hypochloremia The other electrolytes apart from sodium and chlorine are usually not affected Reduction of total bases is due to an almost equimolar diminution of sodium and is attended by a corresponding fall in the total osmotic pressure These changes occur without simultaneous dehydration In some cases there is a tendency to edema not always associated with hypoproteinemia A serious and

(3) A s m d Sand upp 160 pp 1 186 1945

changes must be due to the base binding power of the proteins Results of special investigations support the theory that the proteins have a variable and labile base binding power which is quite independent of the qualitative and quantitative changes demonstrated by ordinary protein determinations The base equivalent which is dependent on the degree of dissociation may be found reduced in all the pathologic conditions investigated in this study especially cirrhosis of the liver in which the largest negative value for determined acids was found such changes probably occur frequently and in other diseases than those studied In some cases the serum proteins seem not to have been dissociated

The base binding power is dependent on the pH and the location of the isoelectric point In several of the conditions studied this point seems to have been labile and to have moved near the neutral point This must have been the cause of the great variations in total bases with constant values for the electrolytic anions When such variations occur total bases vary with the dissociation of the proteins These changes seem at times to persist far into convalescence The increase in total bases observed in some patients after ingestion of salt was probably due to the same cause Ingestion of salt had variable effects in patients with hyponatremia in some the electrolytes remained unaltered and in others there was a further fall in total bases

Adrenal cortex hormone had no distinct effect on the endogenous electrolyte changes A slight degree of sodium retention occurred with increase in body weight and probably also a slight degree of hemodilution In a fatal case of Addison s disease no signs of deficiency of adrenal cortex hormone were found on any examination at certain times there was a slight reduction of total bases Total bases were not affected by ingestion of salt and adrenal cortex extract but a great sodium retention was manifest in edema and increase of weight The hemodilution was striking

There is no evidence that even the greatest electrolyte

lular and the intracellular fluid system without derangement in the distribution of body fluids Broch observed a few patients in whom immediately before death there occurred a rise of total bases and chlorine in one patient 27 m Eq in a few days without a corresponding dehydration

Observations on *patients with hepatic disease* associated with ascites showed electrolytic changes similar to those in febrile diseases Some of the patients with considerable ascites were frequently tapped with loss of large quantities of salt since they had been living for some time on a low salt diet a negative salt balance arose with a fall in total bases and chlorine Ingestion of *sufficient salt increased the electrolyte content* but such large amounts were required to restore normal values that there was considerable increase in the ascites and at times edema

There is reason to believe that the low total base values in these cases are not due solely to loss of salt from the tapping of the ascitic fluid In hepatic diseases without ascites especially in cirrhosis similar changes may be also found

In cases of cirrhosis observed by the author there was generally a reduction in total bases without a significant decrease in *chlorine In acute hepatitis the electrolytes* were practically normal In both febrile and hepatic diseases spontaneous variations of the total bases occurred with corresponding changes in osmotic pressure

In cardiac insufficiency there was generally only a slight reduction of total bases without change in the chlorine content The same condition was observed in cachexia there was no correlation between degree of cachexia and electrolyte changes

In several patients apparently large derangements of the acid base equilibrium were observed The nondetermined acids (phosphate *sulfur and organic acids) should* normally amount to about 8 m Eq (difference between total bases and determined acids) In many patients low or negative values (*—127 m Eq*) were *found The*

changes can evoke the symptoms of the salt deficiency syndrome so long as there is no dehydration Neither the electrocardiogram nor the blood pressure is affected by the hyponatremia The sodium and the chlorine ion therefore must be regarded as biologically indifferent It is also of no importance for the organism that the osmotic pressure is maintained within the normal range even considerable osmotic hypotension may exist without evident symptoms and signs which can be proved to be due to the reduced osmolar concentration In clinical practice electrolyte determinations have served as a basis for quantitative therapy but since it has been proved that disturbance of electrolyte and of water balance can arise independently of the other such determinations are of slight value as a basis for salt therapy

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